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THE CHEMOTHERAPY OF MALIGNANT DISEASE*

BY

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Sir Walter Langdon-Brown was my first teacher of medicine and my father's first teacher of physiology. He was, as many will recall, a physician remarkable for his erudition, his culture, and the breadth of his interests; nevertheless, the topic which I have chosen is not one with which he concerned himself. The very word "chemotherapy" was not in common usage during his professional life; the treatment of malignant disease was surgery, radiotherapy, and morphine; to have suggested that any other methods were worthy of respectful consideration would have been thought visionary by the profession at large and impertinent by the surgeons. There can be no doubt, however, that the advances the last few years have seen in the pharmacological attack on cancer would have fascinated one of the first to appreciate the importance of the chemical approach to clinical medicine and therapeutics.

This lecture is concerned with chemotherapy in its most exact sense, and the treatment of cancer with hormones and with radioactive isotopes is outside its scope. In it the terms "cancer" and "malignant disease" are used interchangeably to indicate proliferative lesions which display autonomous, continuous, and invasive growth. The proliferation is usually rapid and the constituent cells often show anaplasia, or an appearance which suggests, possibly incorrectly, that reversion to a more primitive type has taken place. This definition is broad enough to embrace not only such diseases as carcinoma of the breast and stomach but also leukaemia and even Hodgkin's disease. Current opinion demands their inclusion; cancer must now be defined in terms of dynamic cell behaviour and not by the static morphological criteria of the paraffin section.

Theoretical Considerations

Therapeutic advances are seldom the product of logical reasoning. They are more commonly the result of haphazard empiricism, often based on false assumptions. The use of salicylates in the treatment of rheumatic fever by Maclagan in 1876—a story Langdon-Brown enjoyed telling, for it appealed to his sense of the ironic—is the classic example of how progress in treatment is made. Maclagan believed that, in the orderly Victorian universe in which he lived, the natural remedy for each disease was to be found where that disease was prevalent. Noting the frequency both of rheumatic fever and of the willow tree in marshy country, he was led to use the salicin obtained from the second in the treatment of the first. After the first empirical leap in the dark, progress comes from working backwards, analysing the reasons for success, and building upon this more solid foundation. It will be seen that the chemotherapy of malignant disease is following this traditional pattern, and its theoretical basis is largely derived from a rationalization of its successes.

A rational treatment of cancer has for long seemed a forlorn hope, because the "cause" of the disease remains a mystery. Ablative surgery, where applicable, does not, of course, fall within the description of rational; although often the best that can be offered in the circumstances, it is always a tacit admission of failure. Much of the defeatism which surrounded this problem was due to aiming too high and to fixing attention on discovery of the ultimate cause. Ultimate causes, by definition, never can be found.

It has been customary when contemplating a malignant growth to think of it in terms derived from the study of inflammatory processes: to assume, that is to say, that it represents a reaction on the part of the tissues to some external agent. Reflection reveals no basis for this belief. Whatever may be the initiating cause, the hall-mark of cancer is an alteration in the reproductive behaviour of its constituent cells. Once this new pattern has been acquired it becomes a permanent characteristic. These activities depend upon the genes, and when the mutation which alters cellular reproduction in this fashion has taken place it will perpetuate itself. The cause of this genetic change may be evanescent, but the abnormal pattern of behaviour will have become irrevocably fixed and continuous invasive growth is the sequel. Control of the initiating cause may be necessary for the prevention of cancer, but for its cure a direct attack on the genes is required.

A theoretical approach to this problem would demand knowledge of how the gene transmits its behavioural characteristics. It has long been known that desoxyribose nucleic acid (D.N.A.) is the essential component of the chromosome, and it has been established that structurally different types of D.N.A. exist (Brown and Watson, 1953; Bendich *et al.*, 1953; Chargaff *et al.*, 1953). This demonstration has provided support for the belief that differences in genetic behaviour may depend upon differences in the chemical constitution of the genes. There is, moreover, indirect evidence that the D.N.A. metabolism of healthy and neoplastic cells differs. Malignant and analogous normal cells from the same animal have been grown side by side in tissue culture, and have been shown to differ in their susceptibility to substances known to interfere with nucleic acid metabolism (Biesele *et al.*, 1950). There is therefore some foundation for the view that the malignant behaviour of the cancer cell depends upon the chemical

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structure of its genes, and that this is demonstrably different from that of analogous normal cells.

A parallel has been drawn between the cancer cell and an infecting bacterium (Rhoads, 1956). In a sense, the cancer cell fulfils Koch's postulates: it can always be demonstrated in the lesion in question; it can be cultivated outside the body; and when reinoculated into an animal it will reproduce the disease. A further similarity is to be found in the manner in which both bacteria and cancer cells develop resistance to chemotherapeutic agents initially able to restrain their growth. The analogy breaks down when pressed too far. The immune mechanisms, which are so important in resisting bacterial invasion, do not operate in malignant disease. The cancer cell is not "foreign" in the sense that this description may be applied to the bacterium. Nevertheless, the parallel provides a helpful basis for chemotherapeutic research.

The metabolism of bacteria differs greatly from that of their hosts, and one such difference is responsible for the therapeutic success of sulphanilamide. Investigation of its mode of action provided the invaluable concept of the antimetabolite (Woods, 1940). If the metabolism of cancer cells differs sufficiently from that of healthy tissues, it should be possible to find a substance which will block some metabolic pathway essential to the survival of the first, but unimportant to the second. For reasons already considered, it is logical to regard nucleic acid metabolism as the most promising target for attack, and there is some evidence that in this respect cancer cells and healthy cells may differ. There is therefore no theoretical reason why an agent which will exert a selective toxic action on the cancer cell should not be devised.

Such reflections are responsible for the hope and enthusiasm which now illuminate this problem. Research and the clinical trial of new chemotherapeutic agents proceed with ever-increasing momentum. Developments have been along two main lines. The first is largely empirical. Innumerable compounds, structurally related to those known to have some effect in malignant disease, have been synthesized, their action in selected animal tumours observed, and, if they appear to hold promise, clinical trial made after due pharmacological study. The second aims at the production of substances which may be expected to interfere with nucleic acid metabolism mainly by antimetabolic effect. These again are subjected to the same process of "screening." The labour and expense entailed before even one promising agent is discovered by these methods are immense and have limited this type of research to a few centres.

Any optimism which the tone of the earlier paragraphs may have aroused is sternly corrected by consideration of the results so far obtained in the treatment of human malignant disease. It has been said that the chemotherapy of cancer is in its "presulphonamide stage." It must be admitted that no patient has yet been cured by chemotherapy and that there are only certain tumours which show even a temporary response. These are, in the main, such systematized neoplastic disorders as leukaemia and reticulosarcoma, with occasional instances of other disseminated cancers. The selectivity of the agents at present available is but slight, and their toxic action is shown almost indifferently by malignant and by healthy cells. It is therefore only in tumours which present a wide front to their attack that any effect is to be expected. Moreover, the difficulties of clinical trials are considerable. No patient in whom cure, or even palliation, is likely to be obtained by conventional methods can justifiably be treated by chemotherapy. In consequence, therapeutic trials are limited to patients with leukaemia, reticulosarcoma, and Hodgkin's disease, and to those with inoperable and disseminated malignant disease.

The chemotherapeutic agents which have been shown to exert some beneficial effect upon human cancer fall into two broad groups. These are the cytotoxic drugs and the antimetabolites. The mode of action of the first is uncertain, and they are assumed to exert their effects directly upon the nucleic acids of cell nuclei. The general notion believed to underlie the action of the antimetabolites is now well recognized.

CYTOTOXIC DRUGS

The cytotoxic drugs in common use are certain alkylating agents and a heterogeneous collection of which the mode of action is little understood:

Alkylating Agents: 1. The Nitrogen Mustards

Foremost among the alkylating agents are the nitrogen mustards, amine derivatives of mustard gas containing two beta-chloroethyl groups linked, not by a sulphur atom as in the original compound, but by one of nitrogen. Their therapeutic use is a direct outcome of research into their systemic effects when used as a weapon of chemical warfare. There were, however, earlier indications which, seen in retrospect, might have pointed the way. Mustard gas was noted to exert a profound effect on the haemopoietic system as long ago as 1918 (Stewart, 1918; Krumbhaar, 1919) and to inhibit the appearance of the tumours which follow the repeated application of tar to the skin of the mouse (Berenblum, 1929). Indeed, attempts to treat carcinoma of the breast with it were made by Adair and Bagg (1931), but were abandoned because of difficulties of administration.

During 1942 and 1943 renewed study of the nitrogen mustards again revealed their ability to depress haemopoiesis, and led two groups of workers to investigate their effects upon patients with leukaemia and related disorders (Gilman and Philips, 1946; Wilkinson and Fletcher, 1947). The compounds used were the methyl-bis and the tris beta-chloroethylamine hydrochlorides. The second of these has now been discarded by most workers because of its undesirable side-effects; the first may be regarded as the prototype of the nitrogen mustards in clinical use to-day.

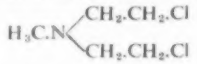
The activity of these substances, both against proliferating cells *in vivo* and in the test-tube, depends upon their reactive 2-chloroethyl radicals (Philips, 1950; Ross, 1953; Stock, 1954), and these properties are particularly evident in compounds possessing two or more such groups. In the body, or in solution, the nitrogen mustards undergo an intramolecular cyclization with the formation of ethyleneimonium compounds which are highly reactive on account of their alkylating capacity, and attack nucleo-proteins by combining with various of their component radicals such as carboxyl, phosphoryl, or amino groups (Ross, 1953).

Once it was appreciated that the cytotoxic effect of these drugs depended upon their 2-chloroethyl groups, a number of analogues were prepared in which the N-methyl group was replaced by other substituents. These alterations affect solubility and possibly distribution within the body, thus determining to some extent the tissue or cell type which will bear the brunt of the cytotoxic attack. A great number of these analogues have been synthesized, but few have proved to possess greater value than the original HN2. Those that deserve mention are R48, the beta-naphthyl compound; R151, or beta-naphthyl-di-(2-chloropropyl)amine; and CB1348, or chlorambucil, a phenylbutyric acid mustard. Russian workers claim good results with several chloroethylamines not in use in other countries; these include

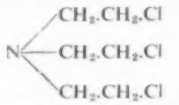
embichin, a methylamine mustard; novoembichin, a 2-chloropropyl derivative; dopan, a pyrimidine compound (Larionov, 1956); and sarcolysine (Larionov *et al.*, 1955), a phenylalanine mustard, an isomer of which had been synthesized independently in England. In Japan, an oxide of HN2, known as nitromin, has been used extensively (Ishidate *et al.*, 1951; Kimura *et al.*, 1952; Kurokawa, 1952). The varying solubilities of the different nitrogen mustards determine the doses which may be administered and the routes by which they may be given. There is little conclusive evidence that their activities against specific types of malignant disease differ in a way which cannot be accounted for by these factors.

Methyl bis-(beta-chloroethyl)amine hydrochloride, or HN2 (Fig. 1), has now been in use for 15 years (Goodman

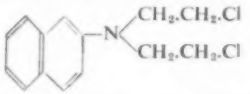
Methyl bis(beta-chloroethyl)amine hydrochloride (HN2).



Tris(beta-chloroethyl)amine hydrochloride (HN3).



Beta-naphthyl-di-2-chloroethylamine (R48).



Beta-naphthyl-di-(2-chloropropyl)amine (R151).

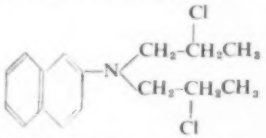


FIG. 1.—Nitrogen mustards.

et al., 1946; Wilkinson and Fletcher, 1947), and its value and limitations are well established. Its solubility necessitates its intravenous administration; injection has to be made as soon as the drug is dissolved, because of the rapid changes it undergoes in solution. The usual dosage is 0.1 mg. per kg. body weight repeated on four successive days. Nausea, vomiting, and anorexia are common three hours after injection and may last 24 hours or longer. Personal experience has shown that the whole dose of 0.4 mg. per kg. may be given at one injection without more severe disturbance than occasioned by each smaller dose; this method is now adopted as a routine. Its effect on the bone marrow is shown by a fall in the leucocyte and platelet counts, which reach their lowest levels about the eighteenth day and recover within four weeks. A second dose should not be administered for six weeks.

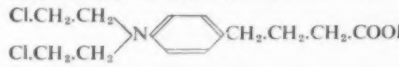
Its clinical applications have been reported by many workers (Gilman and Philips, 1946; Goodman *et al.*, 1946; Jacobson *et al.*, 1946; Karnofsky *et al.*, 1947; Wilkinson and Fletcher, 1946; ApThomas and Cullumbine, 1947; Wintrobe *et al.*, 1947). It has a clearly defined place in the treatment of Hodgkin's disease, particularly in the generalized stage of the disorder when systemic symptoms are prominent; improvement is, however, usually short-lived, seldom lasting more than eight weeks. It will induce remission in chronic myeloid leukaemia, but in general is less satisfactory as a method of control than many others. In chronic lymphatic leukaemia and reticulosarcoma the results are variable and less good than in Hodgkin's disease. Improvement has been noted in bronchial carcinoma, occasionally in disseminated carcinoma of the breast, and sometimes in carcinoma of the ovary.

R48 (erysan, chloronaftina) (Fig. 1) was introduced by Haddow *et al.* (1948). Several clinical trials have been reported (Matthews, 1950; Galton, 1951; Iverson and Meulengracht, 1951; Gardikas and Wilkinson, 1951; Videbaek and Kaae, 1954). Remission has been obtained in Hodgkin's disease, chronic myeloid and lymphatic leukaemia, and polycythaemia vera. It has the advantage of oral administration, but most workers agree that it is in no way superior to HN2, and that myelotoxic effects are more severe.

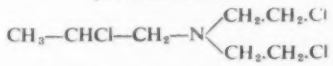
R151 (Fig. 1) was synthesized by Everett and Ross (1949). Good results were reported when used in combination with urethane in myelomatosis (Innes and Rider, 1955). Personal experience does not support these claims, and there are no data concerning its use alone in other malignant diseases.

CB1348, or chlorambucil (Fig. 2), was prepared by Everett *et al.* (1953) and proved effective against the Walker

p-di(2-chloroethylamino)phenylbutyric acid (CB1348).



2-chloropropyl-di(2-chloroethyl)amine hydrochloride (novoembichin).



2 : 6-dioxy-4-methyl-5-(2-chloroethyl)aminopyrimidine (dopan).

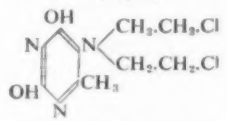


FIG. 2.—Nitrogen mustards.

rat carcinoma (Haddow, 1952). It is given orally in doses of 0.1–0.2 mg. per kg. for periods of four to six weeks. Extensive clinical trials have been reported (Galton *et al.*, 1955; Bouroncle *et al.*, 1956; Ultmann *et al.*, 1956; Farber *et al.*, 1956; Bernard *et al.*, 1956; Hansen, 1957). Its particular value is in the treatment of chronic lymphatic leukaemia, in which remissions are claimed by some observers in as high a proportion as 70%, although personal experience would regard this figure as optimistic. Similar results have been obtained in lymphoid follicular reticulosis, but the results in Hodgkin's disease and reticulosarcoma are less good than with HN2. It has the advantage of rarely causing gastro-intestinal upset.

Embichin, Novoembichin, and Dopan (Fig. 2) are products of Russian workers (Larionov, 1955). Excellent results are reported of their effects in Hodgkin's disease. *Sarcolysine* (Fig. 3) has also been synthesized by this group,

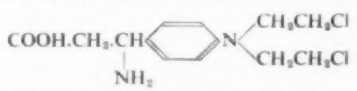


FIG. 3.—Di-2-chloroethyl-*p*-aminophenylalanine (sarcolysine, CB3025, melphalan)

and has proved valuable in their hands in disseminated seminoma and in hepatoma (Larionov *et al.*, 1955; Perevodchikova, 1956; Larionov, 1956). The laevo-isomer of this substance, CB3025, or melphalan, has been used in this country with results which have yet to be assessed.

Nitromin (Fig. 4), an oxidation product of HN2, was first prepared by Stahmann and Bergmann (1946). It has been used extensively in the treatment of malignant disease in

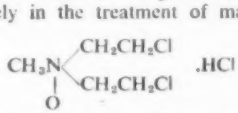


FIG. 4.—Methyl-*bis*(beta-chloroethyl)amine-N-oxide hydrochloride (nitromin).

Japan (Ishidate *et al.*, 1951 ; Kimura *et al.*, 1952 ; Kurokawa, 1952). Its effects are similar to those of HN2, but toxic reactions are said to be fewer. Benefit is reported in Hodgkin's disease and temporary improvement in rhabdomyosarcoma, neuroblastoma (Farber *et al.*, 1956), and occasionally in disseminated carcinoma (Stoll, 1956).

A final compound deserving mention is *hemisulphur mustard* (Fig. 5), a derivative of mustard gas itself, and

FIG. 5.—2-Chloro-2'-hydroxydiethylsulphide (hemisulphur mustard).

interesting in that it contains only one alkylating group. It has been used in advanced carcinoma (Seligman *et al.*, 1952 ; Rutenburg and Seligman, 1956). Side-effects are severe, but about 50% of patients showed significant benefit ; the response was particularly favourable in those with carcinoma of the ovary.

2. The Ethyleneimines

The observation that nitrogen mustards rapidly underwent changes in solution with the formation of ethyleneimonium compounds led to the investigation of other substances of related chemical structure.

The first of these was *triethylene melamine* (tretamine, or T.E.M.) (Fig. 6), a compound long in use in the textile trade

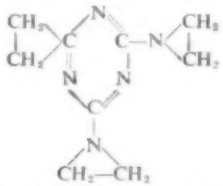


FIG. 6.—Triethylene melamine, tretamine (T.E.M.).

for improving the finish of rayon fabrics. Pharmacological and animal studies showed it to possess anti-neoplastic activity (Philips and Thiersch, 1950). Reports on its therapeutic value in human malignant disease rapidly followed (Wright *et al.*, 1950 ; Karnofsky *et al.*, 1951 ; Hansen and Bichel, 1951 ; Rundles and Barton, 1952 ; Kravitz *et al.*, 1952 ; Bayrd *et al.*, 1952 ; Silverberg and Dameshek, 1952 ; Paterson *et al.*, 1953 ; Axelrod *et al.*, 1953 ; Blackburn and King, 1954 ; Hambly and Robertson, 1955). Although originally given by intravenous injection, T.E.M. is now usually administered orally. Dosage varies ; a method which has proved safe is to give 2.5 mg. daily for two or three days and repeat the dose in a week if the leucocyte and platelet counts have not fallen significantly. Further dosage is regulated by changes in the blood picture. The average amount required is 35 mg. over a period of six weeks or less. It is administered fasting and followed by an alkaline draught.

Results similar to those given by HN2 are obtained in Hodgkin's disease and chronic myeloid leukaemia, but in chronic lymphatic leukaemia and lymphosarcoma they are somewhat better. Improvement has been noted in mycosis fungoides, carcinoma of the ovary, and lymphoepithelioma of the nasopharynx. In combination with irradiation, recession has been reported in retinoblastoma (Reese *et al.*, 1955).

A number of related substances, the *phosphoramides*, have been prepared. Those subjected to clinical trial are the triethylene, the diethyl-diethylene, the 3-oxypentamethylene, and the triethylenethio compounds, known respectively by

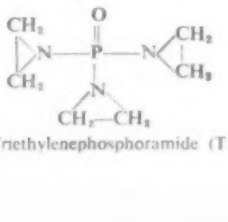


FIG. 7.—Triethylenephosphoramide (T.E.P.A.)

the code names T.E.P.A., D.E.P.A., O.D.E.P.A., and thio-T.E.P.A. The actions of all are similar, but D.E.P.A. and O.D.E.P.A. have been discarded as too unstable and toxic. With T.E.P.A. (Fig. 7) clinical benefit was noted in Hodgkin's disease, in neuroblastoma, and in several patients with disseminated melanoma (Farber *et al.*, 1953 ; Sykes *et al.*, 1953). It has been displaced now by thio-T.E.P.A. (Fig. 8), which is more stable and has a similar range of

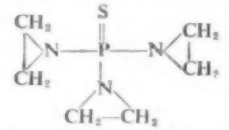


FIG. 8.—Triethylene thiophosphoramide (thio-T.E.P.A.).

action (Shay *et al.*, 1953 ; Leonard *et al.*, 1956), in addition to having some effect in carcinoma of the breast and ovary (Shay and Sun, 1955 ; Bateman and Carlton, 1956 ; Bateman and Larsen, 1956). Thio-T.E.P.A. is given by mouth in doses of 5–10 mg. daily until clinical improvement or evidence of bone-marrow depression appears.

A related sulphonamide, B.E.P. (Fig. 9) (Hendry *et al.*, 1951), has been found to provoke remission in a proportion

FIG. 9.—1,3-*bis*(ethyleneiminosulphonyl)propane (B.E.P.).

of patients with chronic leukaemia (Paterson and Kunkler, 1954). More recently, ethyleneimino-benzoquinone has been used in malignant disease (Wolf and Gerlich, 1956), and useful results are claimed in chronic lymphatic leukaemia and reticulosarcoma (Bernard *et al.*, 1957).

3. The Methanesulphonyloxy Alkanes

The observation that certain of the methanesulphonyloxy alkanes possessed the power of biological alkylation (Haddow and Timmis, 1951) led to the study of this group of compounds, one of which, *busulphan* ("myleran") (Fig. 10) (Haddow and Timis, 1953), was noted to have a

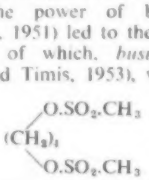


FIG. 10.—Dimethanesulphonyloxybutane (busulphan).

selective action upon the granular leucocytes of the experimental animal (Elson, 1955). Later, clinical trials proved it effective in chronic myeloid leukaemia (Galton and Till, 1955), although inactive against almost all other neoplasms. Subsequent reports have fully confirmed these claims (Consoli and Napoli, 1955 ; Haut *et al.*, 1955 ; Pribilla and Stollberg, 1955 ; Soares and Valente, 1955 ; Blackburn *et al.*, 1956 ; Galton, 1956 ; Louis *et al.*, 1956 ; Schilling and Meyer, 1956). The drug is administered by mouth. The usual dosage is 0.06 mg. per kg. daily. The blood picture returns to normal over four to eight weeks and the spleen shrinks. Maintenance treatment is continued at a level which will preserve a normal platelet count and not depress the leucocytes below 10,000 per c.mm. Remissions have been maintained for upwards of three years. Toxic side-effects are almost unknown, but, unless control is scrupulous, myeloid aplasia may occur.

The octane (Galton, 1956) and the nonane (Sykes *et al.*, 1956) analogues of busulphan have been submitted to trial, but have proved less active and more toxic.

Other Cytotoxic Agents

1. Urethane, or ethylcarbamate, long known to retard the growth of seedlings (Lefèvre, 1939), was later found to inhibit mammary carcinoma in mice (Haddow and Sexton, 1946). Clinical trials proved it an agent capable of inducing remission in chronic myeloid leukaemia (Paterson *et al.*,

1946; Cooper and Watkins, 1950) and of occasional benefit in prostatic carcinoma (Huggins *et al.*, 1947). It is used little now except in myelomatosis, either alone (Alwall, 1947; Rundles *et al.*, 1949) or in combination with R151 (Innes and Rider, 1955). In this disease its effects are difficult to assess, but seldom appear impressive.

2. *Colchicine Derivatives.*—*Demecolcine* or *deacetylmethylcolchicine*, an alkaloid derived from extracts of *Colchicum autumnale* (Santavy and Reichstein, 1950), and a related product, *N-deacetylthiocolchicine* (Velluz and Muller, 1954) are both capable of causing remission in chronic myeloid leukaemia (Moeschlin *et al.*, 1953; Leonard and Wilkinson, 1955). The second is said to be useful in combination with irradiation in the treatment of carcinoma (Huguenin *et al.*, 1955). In my hands demecolcine has been a difficult drug to manage, and its frequent toxic side-effects have led me to abandon it. Other workers endorse this view (Bousser and Christol, 1955).

3. *The Actinomycins.*—An antibiotic known as actinomycin A was isolated from cultures of *Streptomyces antibioticus* as long ago as 1940 (Waksman and Woodruff, 1940), but proved too toxic for therapeutic use. Actinomycin C, a product of *Streptomyces chrysomallus* (Brockmann and Grubhofer, 1949), has undergone extensive clinical trials in France and elsewhere (Croizat and Lacoste, 1955; Olmer, 1955; Tapie, 1955; Gilbert and Thommen, 1955; Ravina and Pestel, 1955). Cytopenia and gastro-intestinal disturbances are common results of its administration, and, although transient remissions may occur in Hodgkin's disease, it is less effective than HN2. Actinomycin D has been investigated and some promising results have been reported (Farber, 1955). It is possible that the actinomycins produce their effects by antimetabolic action.

THE ANTIMETABOLITES

The notion of the antimetabolite is derived from studies of the ability of sulphonamide to inhibit bacterial growth (Woods, 1940). Sulphanilamide bears a close chemical resemblance to *para*-aminobenzoic acid, a nutriment essential for the survival of the streptococcus; by virtue of this similarity it is able to compete with it as a substrate in the enzymatic processes of bacterial metabolism. Because of its higher concentration, sulphanilamide is the successful competitor, but, because it is not identical with the normal substrate, the enzyme reaction cannot proceed to completion and the metabolic pathway is blocked. This concept of competitive inhibition of enzyme reactions has been widely exploited in the chemotherapy of cancer.

The use of antimetabolites in this connexion sprang from two lines of research. A folic acid analogue which had led to regression of mammary carcinoma in mice was unexpectedly found to accelerate the leukaemia process in man (Farber *et al.*, 1947). This observation suggested that folic acid deficiency might have the reverse effect and stimulated the synthesis and study of the folic acid antagonists. The other group of compounds which have established their therapeutic value are the antipurine drugs, and they are the products of a planned study of possible antagonists to the precursors of nucleic acid (Hitchings *et al.*, 1945; Hitchings and Elion, 1954).

Other antimetabolites, aimed at blocking enzyme reactions at different levels in the complex process of nucleic acid synthesis, have been devised; these include pyrimidine, glutamine, amino-acid, and nicotinamide antagonists, but their worth as therapeutic agents is slight.

Folic Acid Antagonists

There are five groups of compounds which exert an effect antagonistic to folic, or pteroylglutamic, acid (P.G.A.). The first to be introduced were *4-hydroxyl derivatives* of P.G.A. (Martin *et al.*, 1947). Their antagonistic action is weak and they proved to have little therapeutic effect in leukaemia (Heinle, 1950). The *4-amino derivatives*, however, were rapidly found to be potent agents (Farber *et al.*, 1948), and representatives of this group have an established place in treatment. These drugs prevent the utilization of folinic acid, or citrovorum factor, as well as inhibit its formation from P.G.A. Those in common use are aminopterin (Fig. 11) and methotrexate or amethopterin (Fig. 12); at

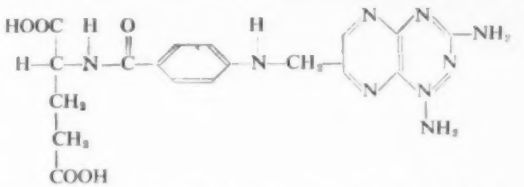


FIG. 11.—Aminopterin (4-aminopteroylglutamic acid).

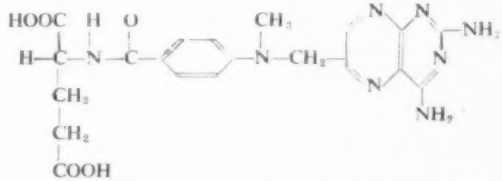


FIG. 12.—Amethopterin, methotrexate (4-amino-N^{10}-methylpteroylglutamic acid).

least four others have been submitted to clinical trial, but in general they offer no advantages over the first two.

Their place in therapeutics lies in the treatment of acute leukaemia in children. Benefit is rare in adults, but in the lymphoblastic type of the disease, and in patients below the age of 15 years, remission is procured in 60–70% (Burchenal, 1952; Fountain, 1954). Some objective effect has been noted in many other forms of cancer, such as rhabdomyosarcoma, Hodgkin's disease, lymphosarcoma, neuroblastoma, and chronic lymphatic leukaemia (Farber *et al.*, 1956).

Aminopterin and methotrexate are given by mouth, the first in daily doses of 0.5–3 mg., and the second of 2.5–10 mg. Toxic effects are common and include ulcerative stomatitis, diarrhoea, vomiting, alopecia, and gastro-intestinal haemorrhage.

The other classes of folic acid antagonist have little therapeutic importance. The *2:4-diaminopteridines* (Daniel *et al.*, 1947) have not been submitted to clinical trial. The *diaminodichlorophenyl pyrimidines*, of which D.D.M.P. (Fig. 13) (Hitchings *et al.*, 1952) is a representative, act in

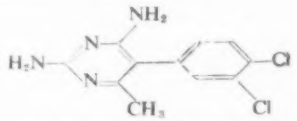


FIG. 13.—2.4-Diamino-5-(3′,4′-dichlorophenyl)-6-methylpyrimidine (D.D.M.P.).

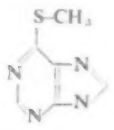
much the same fashion as the 4-amino derivatives of P.G.A., although probably at a different level. They are too toxic for therapeutic use (Murphy *et al.*, 1954). A closely related drug, *diaprim*, originally introduced as an antimalarial, has been found useful in the control of polycythaemia vera (Frost and Jones, 1954). The *dihydrotriazines*, also first synthesized in the search for antimalarials (Carrington *et al.*, 1951; Modest *et al.*, 1952), have not established their clinical utility (Farber *et al.*, 1956).

The ultimate appearance of drug resistance in leukaemia, at first responding to folic acid antagonists, is invariable; when the disease becomes refractory to methotrexate, cross-resistance to all other folic antagonists, including D.D.M.P., develops (Murphy *et al.*, 1954).

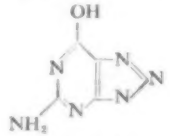
Purine Antagonists

The purine antagonists (Fig. 14) are the fruits of a planned investigation into antimetabolites which might

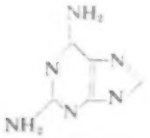
impede nucleic acid synthesis. The first submitted to clinical trial was *2 : 6-diaminopurine*, or D.A.P. (Hitchings *et al.*, 1948), but it proved disappointing (Burchenal *et al.*, 1951), and its place was rapidly taken by 6-mercaptopurine, or 6-M.P. (Elion *et al.*, 1952). Clinical studies with this drug (Burchenal *et al.*, 1953) showed it capable of inducing remission in acute leukaemia and in chronic myeloid leukaemia :



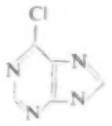
6-Methyl-mercaptopurine



8-Azaguanine

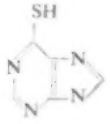


2,6-Diaminopurine

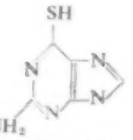


6-Chloropurine

Purine



6-Mercaptopurine



6-Thioguanine

FIG. 14.—Purine antagonists.

occasional improvement has been obtained in reticulosarcoma, but it is of no value in chronic lymphatic leukaemia, Hodgkin's disease, myelomatosis, and various disseminated cancers. It has the advantage over the folic acid antagonists of being effective in adults as well as in children, and the cytological variety of the disease has less influence on the chance of success. The general finding is that, in acute leukaemia, remission is procured in about one-third of the children and one-seventh of the adults treated (Bross, 1954). The drug is given by mouth, in doses equivalent to 2.5 mg. per kg. body weight ; toxic effects other than marrow aplasia are rare. Remission may not be established until after eight weeks of treatment. Its average duration is between four and five months, but in occasional instances it has exceeded a year.

A number of other purine antagonists have been tested clinically. *8-Azaguanine* proved toxic and ineffective (Armistead *et al.*, 1949). *6-Thioguanine* has a similar range of activity to 6-M.P., but offers no advantages over it (Murphy *et al.*, 1955). The same may be said of *6-chloropurine*, with the reservation that the frequency of remission may be somewhat higher in patients over the age of 40 years (Murphy *et al.*, 1955). *6-Methylmercaptopurine* will also induce remission in acute leukaemia, but no extensive clinical trials have been reported (Hall, 1956). *Purine* itself proved unduly toxic (Burchenal, 1956). Finally, *puromycin*, or *stylomycin*, an antibiotic derived from *Streptomyces albo-niger*, has been shown to be a purine antagonist and to be active against animal tumours (Oleson *et al.*, 1955). Clinical trials, however, have proved it ineffective in human disease and to cause renal damage (Wright *et al.*, 1955 ; Burchenal, 1956).

After an interval, acute leukaemia, initially responsive to 6-M.P., becomes refractory, and thereafter the disease is resistant to other purine antagonists. There is, however, no cross-resistance between these drugs and the folic acid antagonists.

Other Antimetabolites

No other antimetabolites have a firmly established place in therapeutics. Of the pyrimidine antagonists, *2-thiouracil* was used some years ago in the treatment of leukaemia, because it had been noted occasionally to cause agranulocytosis in patients with hyperthyroidism. It will sometimes depress the leucocyte count, but seldom leads to clinical improvement (Limarzi *et al.*, 1946). *Amicetin*, an antibiotic with anti-pyrimidine effect, has proved of little value clinically (Tan and Burchenal, 1956).

DL-*Ethionine*, an antagonist of the amino-acid methionine (White and Shimkin, 1954), and *selenium-cystine*, probably a cystine antagonist (Weisberger *et al.*, 1956), have both proved too toxic for use in man.

Azaserine (Fig. 15), an antibiotic derived from a *Streptomyces*, acts as a glutamine antagonist (Hartman *et al.*, 1955). It will induce transient remission in some children

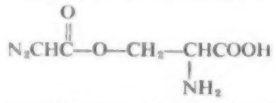


FIG. 15.—O-diazoacetyl-L-serine (azaserine).

with acute leukaemia (Ellison *et al.*, 1954), and there is a suggestion that, used concurrently with 6-M.P., it may increase the frequency of satisfactory response. This possible synergistic effect is under investigation at present.

CONCLUSION

This brief account of some of the agents employed to-day in the chemotherapy of malignant disease suggests that the effort expended by workers in this field has not been rewarded by commensurate achievement. To the clinician, impotent in the face of disseminated cancer, the melancholy catalogue makes disappointing hearing. For him the only yardstick is cure, and he must regard it as unrealistic to be gratified by partial success. Nevertheless, he must reflect that this field has been cultivated for less than twenty years ; that disease processes hitherto unrelentingly progressive may now be halted for a spell ; and that patients desperately ill may for a time be restored to health. During these few years the foundation of a logical approach to the problem has been laid and an efficient machinery for selection and testing of remedies devised. The fruits of these endeavours, if they do little to lighten our task at the bedside to-day, allow us to look with reasoned optimism to to-morrow.

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VIRUS OF ACUTE ENCEPHALOMYELITIS OF MAN AND MULTIPLE SCLEROSIS

BY

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In the spring of 1957 our colleague Dr. R. S. Allison received a request to obtain for patients with multiple sclerosis a vaccine which has been studied in Russia and for which some success had been claimed (Choubladze and Gaidamovitch, 1956a). This vaccine consists of a formolized suspension of the brains of rats or mice which have been infected with the SV strain of a virus of acute encephalomyelitis of man—encéphalomyélite humaine aigue (E.H.A.) (Specification of the State Medical Testing Laboratory, Moscow*). It is manufactured and distributed by the Metchnikoff Institute in Kharkov, where it is called the "vaccine of Margoulis and Choubladze." Before this vaccine was tried in Northern Ireland it seemed desirable to know more about the virus from which it was made and the reasons for using it.

SV Strain of E.H.A. Virus

The E.H.A. virus was recovered in 1942 by Margoulis, Soloviev, and Choubladze in the course of research on the

*"Specification for the preparation and testing of vaccine for the treatment of patients suffering from acute disseminated encephalomyelitis, from disseminated sclerosis, or from a condition brought about by an antigen for intracutaneous diagnostics." State Medical Testing Laboratory, Moscow.

aetiology of multiple sclerosis (Choubladze, Gaidamovitch, and Ivanowski, 1956); five strains of this virus, including the SV strain, were isolated from cases of sporadic encephalitis. The properties and host range of the SV strain have been described by Choubladze *et al.* (1956) and Choubladze and Gaidamovitch (1956b), who showed that E.H.A. virus was immunologically closely related to rabies but that it differed from rabies virus in certain respects. In particular, Negri bodies were never found in the nerve cells of vertebrates infected with the SV strain of E.H.A. There were also other important differences from rabies, such as the symptomatology of infections with E.H.A. virus and its epidemiology. The association of infections with E.H.A. virus and multiple sclerosis was deduced by Choubladze *et al.* (1956) from their observations that "a large percentage" of individuals convalescent from infections with E.H.A. or with multiple sclerosis neutralized the virus of E.H.A., while sera from individuals suffering from other diseases of the C.N.S. failed to do so. Furthermore, Dr. Wolanczi claimed that 50% of patients suffering from multiple sclerosis had antibody to E.H.A. virus (personal communication to Dr. R. S. Allison).

Neutralization Tests

Sera from 50 individuals suffering from multiple sclerosis and from 10 individuals with neurological diseases other than multiple sclerosis were tested for their ability to neutralize the SV strain of E.H.A. virus.

The virus was received from Dr. C. H. Andrewes (National Institute for Medical Research, London) in the form of a lyophilized preparation in an ampoule labelled (in Russian) "Acute virus encephalomyelitis of man—strain 'SV' dried May, 1956." The virus was infective for VSBS mice by the intracerebral route, and mice of this strain (weighing 16–18 g.) were used in all experiments. The incubation period and titres obtained in mice were similar to those described by Choubladze and Gaidamovitch (1956b).

A large pool of infected mouse brain was prepared and aliquots were stored at −70° C. For the neutralization tests 0.2 ml. of undiluted whole serum was mixed with equal quantities of dilutions of infected mouse brain containing 200 and 20 LD_{50} of virus to give a final concentration of 100 and 10 LD_{50} in the test. The virus–serum mixtures were incubated for one hour at 37° C. and for a further hour at +5° C. and were then intracerebrally inoculated in 0.03-ml. amounts into groups each of six mice. Normal control sera from normal rabbits and healthy human beings were used. Immune serum controls consisted of sera from rabbits immunized with the SV strain of virus by the intraperitoneal inoculation of 5 ml. of 10% infected mouse-brain suspension at 0, 3, and 15 days and bled on the 20th day.

In preliminary tests it was found that a few fresh non-inactivated sera from normal healthy human beings and from normal rabbits were capable of protecting a proportion of mice inoculated with virus–serum mixtures containing 10 LD_{50} of virus. In order to detect minimal quantities of any neutralizing antibody which might be present 39 of the 50 sera from patients with multiple sclerosis were tested fresh (or after storage at −70° C.) and after inactivation at 56° C. for 30 minutes against 10 LD_{50} of virus, with the results shown in the accompanying Table. The 50 sera (except one of which there was insufficient quantity to test inactivated serum), both fresh and inactivated, were also tested against 100 LD_{50} of virus.

Results of Tests of Fresh and Inactivated Sera from Patients with Multiple Sclerosis Against 10 and 100 LD_{50} of the SV Strain of E.H.A. Virus

Protection Ratios: No. of Survivors / No. Inoculated	10 LD_{50}		100 LD_{50}	
	Fresh Sera	Inactivated Sera	Fresh Sera	Inactivated Sera
0·6 or 0·5	23	29	43	44
1·6 or 1·5	8	5	7	4
2·6	6	2	0	1
3·6	1	3	0	0
4·6	1	0	0	0
5·6 or 6·6	0	0	0	0
Total	39	39	50	49

It will be seen from the Table that none of the sera tested showed any significant neutralization of 100 LD_{50} of virus. Occasionally a few mice survived which were inoculated with some of the serum–virus mixtures containing 10 LD_{50} of virus (see Table). The amount of inactivation of virus by these sera cannot be accepted as evidence of specific neutralizing antibody, for, as has been noted, we have found occasional sera from normal rabbits and human beings that will similarly inactivate small quantities of this virus.

We also tested sera from 10 individuals suffering from neurological conditions other than multiple sclerosis. The results of these tests with both fresh and inactivated sera were no different from those with sera from patients with multiple sclerosis or from healthy individuals.

Histology

A group of 16 mice were inoculated intracerebrally with 3,000 mouse i.c. LD_{50} of the S.V. strain of H.E.A. virus and two mice were killed daily for histological examination of the brain, cord, and visceral organs.

In those animals killed one to two days after inoculation the brain and cord showed marked hyperaemia but only a very early inflammatory reaction. By the third day the lesions were well established and the picture was that of a widespread meningoencephalitis. The meninges were infiltrated with lymphocytes; perivascular cuffing was a marked feature in both grey and white matter, and particularly in the region of Ammon's horn (Fig. 1). Nerve-cell degeneration, with shrinkage, hyperchromasia, and loss of Nissl substance, was found in the cerebral cortex and other sites, and there was frank necrosis of cells, especially in Sommer's sector. The Purkinje cells were also affected, but the inflammatory infiltration was less intense in the cerebellum. Microglial proliferation with the formation of Babes's nodes was a notable feature in all areas of damage. With Mann's methyl-blue eosin stain and Lendrum's phloxine tartrazine method, acidophilic inclusions of Negri-body type were readily demonstrated in the cytoplasm of the nerve cells, and were best seen at a distance from the most intense inflammatory foci (Fig. 2). Changes in the spinal cord were much less marked than those seen in the hemispheres but were of the same nature. The only visceral lesions noted were hyperplasia of the lymphoid follicles in the spleen,

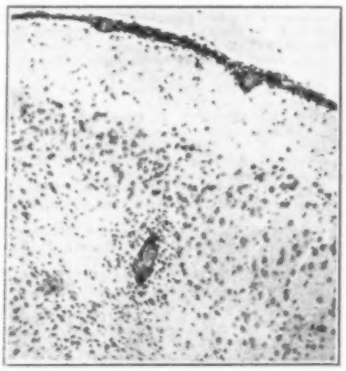

FIG. 1.—Cerebral cortex, with lymphocytic infiltration of meninges and perivascular cuffing. (×100.)

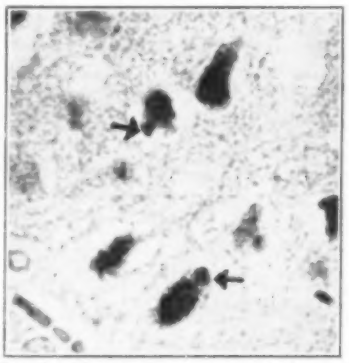

FIG. 2.—Nerve cells with intracytoplasmic inclusions. (Mann's stain. ×1,333.)

and capillary congestion and endothelial swelling in the glomeruli of the kidney.

Discussion

Choubladze *et al.* (1956) have observed that a "large percentage" of patients with multiple sclerosis had antibody to E.H.A. virus. This, in conjunction with other virological studies of E.H.A. virus, led them to believe that there was infection with this virus in some cases of multiple sclerosis. They accordingly used a formolized preparation of E.H.A. virus called the "vaccine of Margoulis and Choubladze" for the treatment of acute encephalomyelitis and multiple sclerosis. This vaccine, which is produced and used in the Soviet Union, is given in two courses, each of divided subcutaneous injections of 24 ml. of the vaccine, or three courses of intracutaneous injections of a total of 5.2 ml. These courses of treatment may be repeated (Instruction*).

We have been unable to find that sera from patients in Northern Ireland with multiple sclerosis show any significant neutralization of the SV strain of E.H.A. virus. The results presented by Choubladze *et al.* (1956) showed that 9 out of 10 patients with multiple sclerosis had neutralization titres ranging from 269 to 2,564. We were unable to obtain information on the exact method of neutralization which was employed by Professor Choubladze and her associates, but the method we employed is the one commonly used to demonstrate antibody to rabies virus and similar to the techniques commonly used to demonstrate antibody to encephalitis viruses.

The results of the studies of Choubladze *et al.* (1956) indicated that E.H.A. virus was immunologically related to rabies virus. They considered that the virus was different from rabies, and they failed to find any Negri bodies in histological material (Choubladze and Gaidamovitch, 1956b). Our demonstration of Negri bodies in mice inoculated with the SV strain of E.H.A. virus and the immunological studies of Choubladze and Gaidamovitch (1956b) seem to indicate that E.H.A. virus cannot be differentiated from rabies virus. (It should be noted that no rabies virus had been handled in our laboratory prior to this investigation.)

Since we cannot find any relationship between the virus of E.H.A. and multiple sclerosis in Northern Ireland, and since this virus cannot be differentiated from that of rabies, there seems to be no rationale for using the "vaccine of Choubladze and Margoulis" in preference to any other rabies vaccine in the treatment of multiple sclerosis.

Choubladze and Gaidamovitch (1956a) claimed that "the vaccine of Margoulis and Choubladze" has produced amelioration in 30% of cases of multiple sclerosis, but Choubladze (personal communication from Dr. R. S. Allison) notes that while their vaccine helps one-third of treated patients it does not help those who have been ill for a long time. Numerous claims have been made for successful treatments for multiple sclerosis. In the assessment of any treatment it must always be remembered that spontaneous remission characterizes early cases. From Brickner's (1936) compilation of recorded results of various treatments of multiple sclerosis, Putman (1939) concluded that 665 out of 1,407 cases (47.5%) profited from the treatments. He also showed that 44% of fresh lesions in untreated patients are capable of a complete functional recovery. If it is assumed that patients usually seek a new form of treatment when a new lesion occurs it is perhaps not surprising that 47.5% of patients given *any kind* of treatment have been reported to show improvement in view of the 44% of spontaneous remissions (Putman, 1939). On this basis there is thus no evidence for the success of the "vaccine of Choubladze and Margoulis." Indeed, the use of this vaccine (formolized rabies-virus-infected rodent brain), which is given in multiple inoculations, might do harm.

*Instruction for the administration of the vaccine against acute encephalomyelitis and sclerosis multiplex. Souischimeaport, Moscow.

Summary

The SV strain of E.H.A. virus which has been used to prepare the vaccine of Choubladze and Margoulis for the treatment of multiple sclerosis appears to be rabies virus.

We were unable to demonstrate any specific neutralization of the SV strain of E.H.A. virus with sera from patients with multiple sclerosis.

Choubladze and Gaidamovitch's (1956a) claim for amelioration of 30% of patients with multiple sclerosis treated with this vaccine is of the same order as that of spontaneous remissions (44%) of fresh lesions in untreated patients.

The possible danger associated with the use of any rabies vaccine may make the use of the "vaccine of Choubladze and Margoulis" dangerous in the treatment of multiple sclerosis.

We wish to thank Dr. R. S. Allison for the personal communications and, in collaboration with Dr. J. H. D. Millar, for arranging for the collection of the human sera; and M. le Médecin Colonel Grizaud, Chef du Centre de Documentation de Médecine Tropicale, for the MS. of Professor Choubladze and Dr. Gaidamovitch abstracted in *Méd. trop.*, 1956, **16**, 712.

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AMISOMETRADINE, A NEW ORAL DIURETIC

BY

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Much importance is attached to the search for an orally active diuretic to support or replace parenteral mercurial preparations in the management of cases of heart failure. To date, all such drugs have had in common the disadvantage of poor gastro-intestinal tolerance when given in effective doses.

Of the active diuretics in the amino-uracil series of drugs, aminometradine ("mictine") has been most widely investigated (Kattus *et al.*, 1952; Platts and Hanley, 1956). In effective doses it has at least half the diuretic strength of mersalyl, but such doses produce epigastric discomfort, nausea, vomiting, or diarrhoea in almost 50% of patients; headache, tinnitus, and albuminuria are less common side-effects. Several chemically similar drugs have been studied, and amisometradine ("rolicton"*) is the most promising of them at present. In animals it has an equal or a better diuretic action than aminometradine, but causes far less vomiting; in both long and short trials it has been found relatively

*Kindly supplied by G. D. Searle and Co., Ltd.

free from toxic effects (Hambourger *et al.*, 1957; Van Arman *et al.*, 1957). Reports of three brief clinical trials in America were encouraging, and suggested that amisometradine was superior to all other oral diuretics (personal communications from H. Gold in February, 1956; M. G. Golder in June, 1956; and E. Settel in June, 1956).

The purpose of this paper is to report our own experience with amisometradine in the treatment of heart failure, its diuretic strength being compared with that of mersalyl, and particular attention being paid to the incidence of gastro-intestinal intolerance.

Method

Twenty patients who were admitted to hospital for treatment of heart failure were chosen for the trial. Sixteen of them had a raised venous pressure and oedema, and four had pure left ventricular failure. The aetiology was rheumatic in 11 cases, ischaemic in 7, and congenital in 2. Sixteen had previously been taking full doses of digitalis, and 12 had received regular injections of mersalyl in addition.

During the period of the trial digitalis was continued, dietary sodium was restricted to 1 g. daily, and the fluid intake was fixed at either 40 or 50 oz. (1,136 or 1,420 ml.) daily. The 24-hour urine output and body weight were measured daily and charted.

Test doses of amisometradine and mersalyl were given alternately to each patient at intervals of three to four days. The tests were grouped in pairs, so that each amisometradine test was accompanied by a mersalyl test in the same patient at only a short interval, during which time the patient's clinical condition had changed very little. To avoid influencing the results by the spontaneous diuresis which often occurs a few days after a patient is put to bed in hospital, the trial was not begun during the first 10 days of admission in a proportion of cases, and in the remainder amisometradine was administered first in one half, and mersalyl first in the other half. Six of the 20 patients came into the latter group, and thus three pairs of tests were recorded which favoured one or the other drug. The errors in comparison of the drugs in these six patients individually were considered to balance out when comparison was made over the whole series.

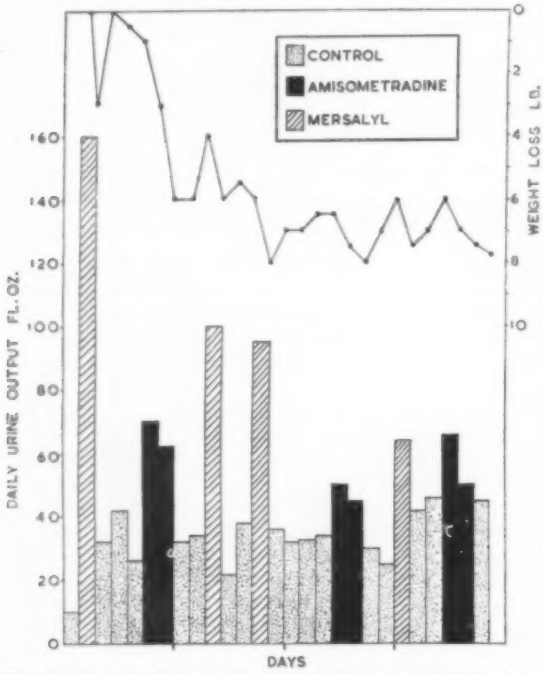

FIG. 1.—Case 8. Urine output and weight, recorded daily in a man aged 43 with congestive heart failure previously untreated. Action of amisometradine and mersalyl compared. (Fluid intake 40 oz. (1,136 ml.) daily.)

Amisometradine was given in a dose of 400 mg. (one tablet) three times daily for two days. Administered in this way, the drug acts over a period of 48 hours (Fig. 1), and its diuretic effect was considered to be the excess of urine passed during this period. As already described in connexion with other amino-uracil derivatives (Spencer and Lloyd-Thomas, 1953; Platts and Hanley, 1956), the diuresis may not begin for 12 to 24 hours after the first dose is administered, and may continue for an equal time after the last dose. The 48-hour period of diuretic activity was therefore taken to be either the first and second days, as in Fig. 1, or the second and third days, as in Fig. 2, whichever yielded the greater quantity of urine. This selection of two out of the three days gave a figure slightly less than the total diuresis obtained, but no more rigid ruling served our purpose better.

In the case of mersalyl, a dose of 2 ml. intramuscularly was given, and the diuresis was considered to be the excess of urine passed during the 24 hours immediately following the injection.

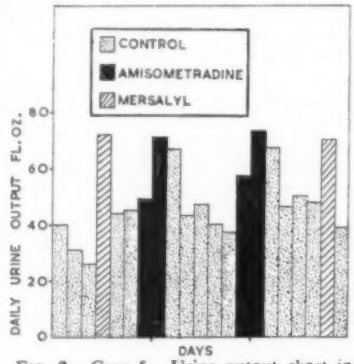

FIG. 2.—Case 5. Urine output chart in a man aged 56 with congestive heart failure. Amisometradine and mersalyl compared. Action of amisometradine delayed 24 hours after administration. (Fluid intake 50 oz. (1,420 ml.) daily.)

The excess of urine passed was estimated in each case by subtracting from the output during the period of diuresis the output during the control period immediately preceding the test, during 48 hours in the case of amisometradine, and during 24 hours in the case of mersalyl. The changing physiological state of the patient prohibited use of a mean output calculated from all control days as a basis from which to measure diuresis.

The diuresis recorded in each test was expressed as a percentage of the output during the preceding control period, and this figure was called the diuretic index for that test. For example, if an amisometradine test resulted in an output of 140 oz. (3,975 ml.) over 48 hours, and the output during the preceding 48 hours was 80 oz. (2,270 ml.), then the diuresis was expressed as 140−80, or 60 oz. (1,700 ml.), and the diuretic index as 60/80×100 or +75%. The diuretic index of each drug was averaged for each patient, and only these average indices were used in computing the results for the whole series.

Side-effects, if any, were recorded, and their specificity was verified. In most cases a daily specimen of urine was tested for albumin. Routine blood and full chemical and microscopical urine examinations were repeated at the end of the trial period.

Finally, three additional patients in need of diuretic therapy were given amisometradine 400 mg. three times daily for periods of 10 to 14 days, with repeated observation of their clinical response, the white blood cell count, blood urea, serum electrolytes, and urine.

Results

In each patient one or more pairs of amisometradine and mersalyl tests were performed. The table shows the average diuresis and diuretic index of each drug in each of the 20 patients. In six of them (Cases 6, 8, 9, 13, 14, and 18) the

results were influenced by the advantage given to the drug that was given first. The average figures at the foot of the table represent the results of 38 tests of each drug, and provide a direct measure of the diuretic strength of amisometradine in terms of that of mersalyl.

Diuretic Strengths of Amisometradine 400 mg. t.d.s., for Two Days, and Mersalyl 2 ml. Intramuscularly, Compared in 20 Patients

Case No.	No. of Tests	Average Diuresis				Diuretic Index (%)	
		Amisometradine		Mersalyl			
		oz.	ml.	oz.	ml.	Amisometradine	Mersalyl
1	1	44	1,250	36	1,023	+52	+90
2	4	31	880	18	511	+70	+69
3	5	34	966	34	966	+42	+84
4	1	32	909	42	1,193	+37	+78
5	2	45	1,278	34	966	+50	+100
6*	2	21	597	16	454	+29	+41
7	1	40	1,136	16	454	+50	+33
8†	3	37	1,051	80	2,272	+52	+220
9†	1	36	1,023	60	1,705	+51	+170
10	2	11	313	8	227	+48	+41
11	2	7	199	42	1,193	+10	+120
12	2	22	625	33	938	+35	+110
13*	1	47	1,335	30	852	+71	+71
14*	2	30	852	21	597	+27	+35
15	1	26	739	44	1,250	+33	+110
16	2	30	852	88	2,500	+49	+260
17	1	35	994	15	426	+35	+65
18†	1	10	284	44	1,250	+11	+150
19	2	12	341	70	1,989	+12	+190
20	2	19	540	14	398	+29	+39
Average		28	795	37	1,051	+41	+103

* Clinical condition improving rapidly; amisometradine given first.
† Clinical condition improving rapidly; mersalyl given first.

In 17 of the 20 patients the diuretic index of amisometradine ranged between +29% and +71%, indicating a satisfactory therapeutic response. In the remaining three it was relatively ineffective, with indices of +10%, +11%, and +12%. The average diuretic index of amisometradine in the 20 patients was +41%, compared with +103% in the case of mersalyl. In other words, 2.4 g. of amisometradine administered over a period of 48 hours had 40% of the diuretic potency of a single injection of 2 ml. of mersalyl. In four patients amisometradine appeared more effective than mersalyl, and this was consistently so on four occasions in Case 2.

The occasional delay in the action of amisometradine has already been mentioned, and is illustrated in Fig. 2. This occurred in about one-third of the patients, and was most marked in cases of severe congestive heart failure, becoming less conspicuous during recovery.

No side-effects attributable to amisometradine were seen in 15 of the 20 patients. Two developed mild nausea on the first day of administration only, but subsequently tolerated the usual dose. In one patient (Case 18) nausea was more severe, and recurred on each day of amisometradine therapy, associated on one occasion with vomiting. This patient had marked distension of the liver, and vomiting had been a prominent symptom of heart failure before admission. Reduction of the amisometradine dose by half improved tolerance, but produced little diuresis. In Case 17 transient mild diarrhoea occurred on the day following the single amisometradine test; unfortunately the test could not be repeated in this patient. Case 19, that of a woman with primary pulmonary hypertension, developed tinnitus and deafness on the second administration of amisometradine; this subsided within 12 hours, but subsequently recurred on two occasions after only 400 mg. of amisometradine, preventing further use of the drug.

In no case did albuminuria develop or increase during the trial. No toxic effect was detected by the full blood and urine examinations. Two patients (Cases 2 and 3) received total doses of 12 and 14.4 g. of amisometradine respectively over a period of six to seven weeks. Their recovery from heart failure was good, there were no side-effects, and the blood count, serum electrolytes, and urine remained unaffected throughout.

Continuous Daily Administration

The object of this trial was to find out whether amisometradine was an active diuretic in doses that were well tolerated. No attempt was made to establish the best scheme of dosage, but it seemed desirable to see whether the drug could be given daily without ill effect, and so this was tried in three patients. The first two were given amisometradine 400 mg. three times daily for 10 days, and their clinical progress suggested that a moderate diuretic effect had been obtained. A third patient in chronic heart failure was given mersalyl injections twice weekly only for the first fortnight, and amisometradine 400 mg. three times daily (together with one mersalyl injection weekly) for the second fortnight. The urine output chart (Fig. 3) shows a good diuretic response to

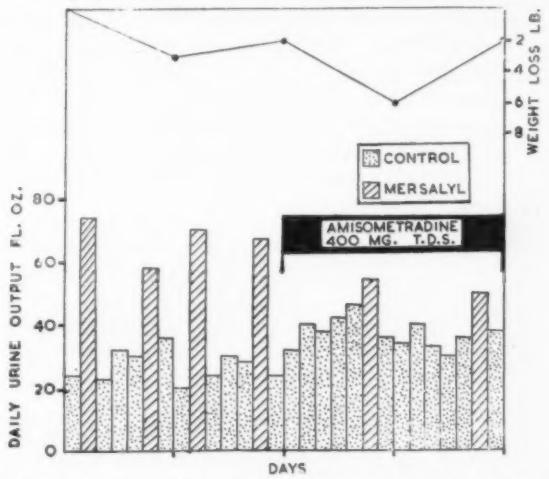

FIG. 3.—Case C. Urine output chart showing the result of adding amisometradine to the treatment of a woman aged 54 in chronic heart failure. Mersalyl twice weekly for the first two weeks, and once weekly with amisometradine 400 mg. t.d.s., for the second two weeks. (Fluid intake 40 oz. (1,140 ml.) daily.)

amisometradine given in this way. No side-effects were observed in these three patients, and no change could be detected in the blood or urine.

Discussion

Early in this study it became evident that amisometradine produced a significant diuresis in most patients with heart failure, and that gastro-intestinal intolerance was unusual. Many difficulties beset the measurement of the diuretic strength of a new drug, as discussed by Spencer and Lloyd-Thomas (1953), but these have been overcome to some extent in the present study by comparing the drug with the already familiar mersalyl. Paired doses of each drug given at short intervals permitted little change in the clinical state of the patient between tests. When such a change did occur, each pair of tests was balanced by another under similar circumstances, in which the order of administration of the drugs was reversed. The results of each test were made still more comparable by the expression of diuresis in the form of a diuretic index, taking into account the rate of urine flow immediately preceding the test.

The final outcome of the trial, that 2.4 g. of amisometradine had only 40% of the diuretic strength of 2 ml. of mersalyl, makes it clear that even the best oral diuretics cannot yet replace mersalyl in the treatment of acute or severe heart failure, but with improved tolerance and greater potency they are becoming increasingly valuable adjuncts.

Amisometradine proved to be greatly superior to aminometradine in the matter of tolerance and was not less potent. In only one patient was nausea troublesome, and she was known to be prone to gastro-intestinal disturbance. The only

other side-effect encountered was tinnitus in one patient; this and other aural disturbances have been described as rare complications of other amino-uracil derivatives.

No toxic effects were observed following the use of amisometradine. In the American reports quoted, skin reactions were rare, and leucopenia was described in one case.

The diuresis produced by aminometradine is accompanied by excretion of sodium and chloride in approximately equal amounts, with a small increase in potassium loss (Platts and Hanley, 1956). A similar loss of electrolytes accompanied by diuresis follows the administration of amisometradine to dogs (Van Arman *et al.*, 1957), and this is presumed to occur in man. The precise mode of action on the kidney is not yet known.

Summary

The effect of amisometradine (rolicton), a new oral diuretic, has been tested in 20 patients with heart failure.

In doses of 400 mg. three times daily over a period of two consecutive days it was found to have 40% of the diuretic potency of 2 ml. of mersalyl intramuscularly.

The drug was relatively free from side-effects, in respect of both gastro-intestinal tolerance and toxic reactions.

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TETANUS IN NIGERIA

REVIEW OF 100 CASES TREATED IN IBADAN

BY

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Tetanus is the third most common cause of admission to the adult medical wards of University College Hospital, Ibadan, being exceeded in frequency only by lobar pneumonia and pulmonary tuberculosis. It is by far the most frequent cause of death in these wards. Of 79 tetanus patients admitted during 1955, 43 died, representing 6% of all admissions and 21% of all deaths in the medical wards. The corresponding figures for 1954 were 77 admissions with 44 deaths. The incidence of tetanus in Nigeria is not known, but from the above figures and the fact that the category of adult, which in this hospital includes anyone over the age of 8 years, probably comprises half the total population (600,000), there are at least 80 cases a year in a population of 300,000. This gives an annual incidence of 26.6 per 100,000, with a mortality of 14.6 per 100,000. In England and Wales in 1951 (Registrar-General, 1953) 81 deaths were attributed to tetanus, a mortality of 0.2 per 100,000; and Hampton (1954), in a review of tetanus in the United States of America from 1947 to 1951, found an annual mortality of 0.2 per 100,000. To what extent the above approximation for Ibadan is applicable to Nigeria as a whole is unknown.

There have been few reports on tetanus from Nigeria. Jeliffe *et al.* (1950) described five cases (three fatal) of puerperal tetanus, drew attention to many factors present in domiciliary midwifery in Nigeria which encourage tetanus, and stressed the need for adequate prophylaxis at parturition for both mother and child. Jeliffe (1950) described 25 cases of neonatal tetanus with only one survival, and again drew attention to the many opportunities of contamination by tetanus spores in the poorer Nigerian home.

The purpose of the present article is to show from observations on 100 cases of tetanus the nature of the disease in a tropical area where the incidence is high, with reference to aetiology, factors influencing prognosis, course of the disease, and response to treatments used. A method of approach to the problem that tetanus presents in such an area is suggested.

Material and Methods

The material under review consists of 100 consecutive adult cases of tetanus treated at University College Hospital, Ibadan, from February, 1954, to May, 1955. Of the 100 cases, 19 occurred between February and May, 1954, and were treated by other members of the staff of the medical unit, while the remaining 81 were treated by me. The data pertaining to the first 19 cases were obtained from the case records.

The following scheme for recording observations was used in the 81 cases which I treated. (1) All patients were personally examined as soon as possible, usually within an hour after admission. (2) A history was taken so far as was possible from the patient, supplemented as necessary by further details from the relatives. (3) After initial examination and assessment, treatment was begun. (4) Records by nursing staff were kept on a specially designed tetanus progress sheet (see Chart). Observations by the medical staff were recorded on the clinical notes. Observations to be entered on the tetanus progress sheet were made when the sedative drugs were given, so that the patient was disturbed as little as possible. Thus the frequency of recorded observations increased with the frequency of administration of sedatives, which was usually in direct proportion to the severity of the case.

General Management and Treatment

When available a special nurse was detailed for each patient, and the bed was placed against the wall in a corner of the ward. Special attention was paid to oral toilet. If possible, patients were given fluids orally and such food as they could take. Drinking was made easier for those with severe trismus by the use of straws. Before May, 1954, the oral fluid intake was supplemented if necessary by the

UNIVERSITY COLLEGE HOSPITAL, IBADAN. Tetanus Progress Chart.

Surname						First Name(s)				Number		
						FLUIDS				URINE		
Date and Time	Temperature	Pulse	Respiration	Spasms	Opisthotonos	Oral	Sub-cutaneous	Intra-venous	Sedation	Output	Chlorides	Haematocrit

rectal route. This proved unsatisfactory, and the following routine was adopted in the 81 cases treated after this date. In severe cases all specimens, and in milder cases daily specimens, of urine were tested for chloride content by Fantus's method. If it was 3 g. per 100 ml. or over the patient was considered to be adequately hydrated. If under 3 g. but over 1 g. per 100 ml. 2 pints (1,140 ml.) of normal saline was given intravenously, and if less than 1 g. per 100 ml. 3 pints (1,700 ml.) was given. The saline was infused rapidly, the first pint (570 ml.) in 20 minutes and the second in 40 minutes, the 2 pints thus taking one hour to give. In those requiring more than 2 pints the rate of infusion was slower. Intermittent infusions of short duration were employed, as careful attention could then be given during the process. Continuous intravenous infusions were not well tolerated. Although solid food was given where practicable, it was felt that patients could survive the major part of their illness on a low calorie intake. Intragastric intubation was attempted as a means of giving fluids, but the passage of the tube sometimes caused severe laryngeal spasm and the method was abandoned.

Penicillin.—All cases were given 300,000 units of procaine penicillin daily intramuscularly as a prophylactic measure against chest infection and in many cases as part of the treatment of the wound. This was continued for 24 hours after the cessation of clonic spasms unless required for further treatment of the wound or complications. It was stopped earlier only if some complication occurred requiring the use of a broad-spectrum antibiotic.

Treatment of Wound.—This was carried out as indicated for the particular wound irrespective of the occurrence of tetanus. Radical excision of tissue was done in one case which followed osteomyelitis of the radius and ulna. In this case the limb was amputated.

Antitetanic Serum.—In 77 cases 100,000 I.U. of antiserum was given as soon as the diagnosis was made (50,000 I.U. intravenously and 50,000 I.U. intramuscularly). Two patients, one of whom was treated entirely as an out-patient, were given 3,000 I.U. of antiserum only. The remaining 21 were not given antiserum; these were not selected, but occurred after it had been decided to stop giving antiserum for a trial period. The cases are fairly evenly distributed as regards their severity.

Sedative Treatment.—In 76 cases paraldehyde, 4–6 ml., and sodium amylobarbitone, 3¼ gr. (0.24 g.), were given intramuscularly in alternate doses. The interval between the doses varied from two to six hours, depending on the condition of the patient. Sedation was aimed at reducing reflex spasms and opisthotonos as much as possible without depressing respiration unduly. In 18 cases chlorpromazine, 15–25 mg. intramuscularly, and sodium amylobarbitone, 3¼ gr. (0.24 g.) intramuscularly, were given simultaneously. The interval between doses varied from three to six hours according to the condition of the patient. Two cases were given chlorpromazine alone for a short time in divided doses up to a total of 300 mg. daily. It did not appear to be controlling the spasms satisfactorily and was therefore abandoned. These two cases are included in the category under which the main part of their treatment was carried out.

Muscle Relaxants.—One patient who died was treated with intravenous thiopentone, gallamine triethiodide, and intermittent positive-pressure respiration, which was performed by means of a manually operated bellows. Four fatal cases were treated with mephenesin given intravenously at a rate which reduced spasms but did not necessitate the use of artificial respiration. It was given in normal saline or 6% glucose in distilled water solution, 3 g. to 1 pint (570 ml.), at a rate of from 0.3 to 1 g. an hour. These cases, which were all severe, became a great problem as regards their fluid balance, since they required up to 25 g. of mephenesin daily and it was felt that it might be dangerous to give more concentrated solutions. All specimens of urine passed by these patients were tested spectroscopically for the presence of haemoglobin and all were negative (Hewer and Woolmer, 1947; Pugh and Enderby, 1947; Murray Parkes, 1954; Docherty, 1955). Mephenesin was used orally (Adriani and Kerr, 1955) in doses up to 9 g. daily in convalescent cases in an attempt to accelerate the rate of reduction of residual stiffness, but as no definite benefit was observed it was abandoned.

Pethidine.—This was used, both orally and intramuscularly, in the later stages of the disease for the treatment of muscular pain and cramp, and was extremely effective.

Physiotherapy.—This was begun as soon as clonic spasms had definitely ceased. It was continued in all cases until discharge from hospital, and, in as many cases as would attend, until all stiffness had gone.

Post-mortem Examination.—This was carried out on only one case. This patient had been treated by complete muscular relaxation with intermittent positive-pressure respiration, and the cause of death was bronchopneumonia.

Analysis of Clinical Material

The series comprised 56 male and 44 female patients: 30 males and 26 females died, the overall mortality being 56%. There is no statistically significant difference in the mortality of the various age groups (Table I).

As no attempt to culture *Cl. tetani* from wounds was made, owing to technical difficulties, the decision on the portal of entry of the organism was made on the history and clinical examination (Table II). The cases following lower-limb injury, which form the largest group, are further subdivided (Table III). The chronic non-specific ulcers had been present for one year in one case, three months in another, and for an average of 14 days in the remainder, except for one case of unknown duration. Guinea-worm infestation is a common cause of ulceration; it occurred in 11 cases (10 in the lower limb and one in the arm).

It is felt that most of these cases in which no causative injury was found probably followed minor foot injuries which had healed before admission. The post-partum cases comprised 18 puerperal cases and 2 following abortion. The five post-operative cases were in hospital at the onset of the disease, and, although treatment was begun within three hours of the onset, all five patients died. Two of the cases occurred at a time when the sterilizing equipment was found to be faulty.

TABLE I.—*Age and Mortality*

Age Group	Lived	Died	Total	Mortality
Under 10	Nil	1	1	100%
10–19	11	9	20	45%
20–29	15	21	36	58%
30–39	9	16	25	64%
40–49	8	8	16	50%
50 and over	1	1	2	50%

TABLE II.—*Portal of Entry of Cl. tetani*

Portal of Entry	Lived	Died	Total	Mortality
Lower limb injury	17	22	39	56%
Post-partum	8	12	20	60%
Post-operative	Nil	5	5	100%
Upper-limb injury	3	1	4	25%
Head and neck injury	1	2	3	66·6%
Otitis media	1	Nil	1	Nil
Vaccination sore	1	..	1	..
Penile sore	1	..	1	..
Not known	12	14	26	54%

TABLE III.—*Types of Injury of Lower Limb Followed by Tetanus*

Type of Injury	Lived	Died	Total	Mortality
Lacerations	6	10	16	63%
Chronic non-specific ulcers	6	4	10	40%
Guinea-worm sore	4	6	10	60%
Chigger flea sore	1	2	3	66·6%

Native applications to sores, including those following vaccination against smallpox, include earth and animal excreta, and must often be responsible for the occurrence of tetanus.

The relation of incubation period to mortality is shown in Table IV. The cases were grouped into those having an incubation period of nine days and over and those having an incubation period of less than nine days, as this division gave the nearest to a significant difference in the mortality ($\chi^2=2.803$, $P=0.09$). Cases in which the causative injury occurred more than one month before the onset of symptoms are not included in Table IV, as the patients' estimate of time intervals of over one month tended to be extremely inaccurate.

Table V shows the relation of period of onset to mortality. The period of onset, which is defined as the time elapsing between the onset of the first symptom and the first generalized spasm, if less than 48 hours indicates a bad prognosis (Cole, 1940; Knott and Cole, 1952). It is usually more accurately measured than the incubation period, as the two events involved occur at a reasonably short time interval and are of such a nature that they are likely to impress the patient or his relatives. There is a significant difference in the mortality of the above groups ($\chi^2=11.38$, $P<0.01$).

The incubation period and period of onset are related to mortality in Table VI. In 19 cases the sum of the incubation period and the period of onset was less than the seven days of Knott and Cole (1952). Only 13 of these patients died, giving a mortality of 68%.

TABLE IV.—*Relation of Incubation Period to Mortality. Assessable in 64 Cases*

Incubation Period	Lived	Died	Total	Mortality
Under 9 days	13	28	41	68%
9 days and over	13	10	23	43%

TABLE V.—*Relation of Period of Onset to Mortality. Assessable in 88 Cases*

Period of Onset	Lived	Died	Total	Mortality
0–48 hours	20	45	65	69%
Over 48 hours	16	7	23	30%

TABLE VI.—*Incubation Period and Period of Onset Related to Mortality. Assessable in 60 Cases*

Incubation Period	Period of Onset	Lived	Died	Total	Mortality
Under 9 days	0–48 hours ..	6	23	29	79%
	Over 48 ,, ..	4	5	9	56%
9 days and over	0–48 ,, ..	7	10	17	59%
	Over 48 ,, ..	5	Nil	5	Nil

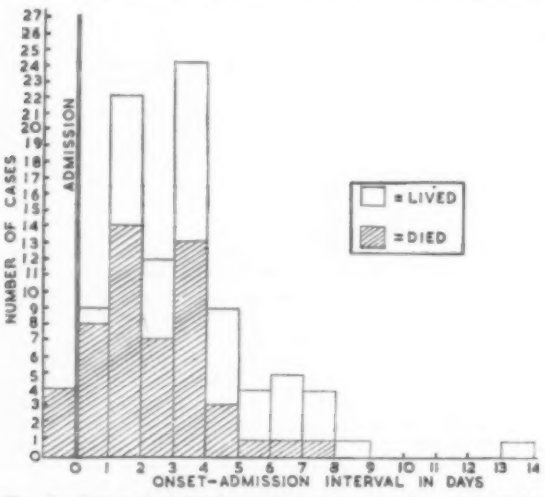

FIG. 1.—Onset-admission interval, showing mortality. Assessable in only 95 cases.

The high mortality among the cases treated early in the disease (Fig. 1) can be partly explained by the fact that severe cases were, on the whole, brought for treatment earlier than milder cases. It would not appear that early treatment, of the type used here, affects the mortality greatly in severe cases.

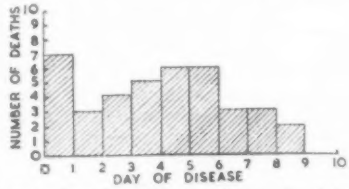

FIG. 2.—Duration of disease in fatal cases, omitting cases in which complications or treatment may have directly caused death, the duration of disease was assessable in 39 cases.

The average interval from onset to death in 39 cases was 4.5 days (Fig. 2). The duration of treatment in these fatal cases is shown in Fig. 3. The high mortality in the first three days after admission can be explained by reference to Figs. 1 and 2. Although the largest single number of deaths occurred on the first day of the disease, many of the cases were not seen until the disease was far advanced.

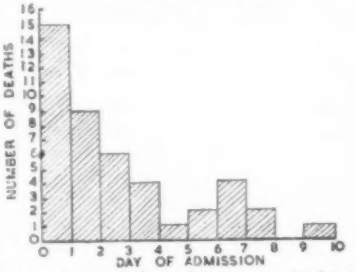

FIG. 3.—Duration of treatment in fatal cases, omitting cases in which complications or treatment may have directly caused death.

The temperatures given in Table VIII are the highest recorded on the patients at any time.

The methods of sedative and relaxant treatment are related to mortality in Table VIII. Table IX shows the mortality in those given and those not given antiserum; Table X shows the mortality in the "antiserum" and "non-antiserum" cases with the period of onset. There is no statistically significant differences in the mortality of those

TABLE VII.—*Maximum Temperature Related to Mortality*

Temperature Range	Lived	Died	Total	Mortality
98·4° F. (36·9° C.) ..	8	3	11	27%
98·5° F.–(37° C.–) ..	7	5	12	42%
101° F.–(38·3° C.–) ..	11	11	22	50%
102° F.–(38·9° C.–) ..	6	8	14	57%
103° F.–(39·4° C.–) ..	8	11	19	58%
104° F.–(40° C.–)	2	9	11	82%
105° F.–(40·6° C.–) ..	2	7	9	78%
106° F. (41·1° C.) and over	Nil	2	2	100%

TABLE VIII.—*Methods of Sedative and Relaxant Treatment Related to Mortality*

Drugs Employed	Lived	Died	Total	Mortality
Paraldehyde and sodium amylobarbitone	37	40	77	52%
Chlorpromazine and sodium amylobarbitone	6	11	17	65%
Intravenous mephenesin ..	Nil	4	4	100%
Thiopentone and gallamine	,,	1	1	100%
None	1	Nil	1	Nil

TABLE IX.—*"Antiserum" and "Non-Antiserum" Cases, With Mortality*

Antiserum	Lived	Died	Total	Mortality
Given	35	39	74	53%
Not given	7	12	19	63%

Two cases which did not have a standard dose of A.T.S. and five cases treated by relaxants have been omitted.

who were given antiserum and those who were not. The two cases which had only 3,000 I.U. of antiserum have been omitted from Tables IX and X.

TABLE X.—*"Antiserum" and "Non-Antiserum" Cases, With Period of Onset and Mortality*

Anti-serum	Period of Onset	Lived	Died	Total	Mortality
Given	0–48 hours ..	17	32	49	65%
	Over 48 ,, ..	15	4	19	21%
Not given	0–48 ,, ..	3	9	12	75%
	Over 48 ,, ..	1	2	3	67%

Assessment was made in 83 cases only; two cases which did not have a standard dose of A.T.S. and five cases which were treated by relaxants being omitted.

Complications

There were four clinically definable cases of bronchopneumonia (all fatal), and one further case was discovered at necropsy. In no other case was clinical evidence of chest infection found, although it is probable that many cases had some degree of such infection.

Four male cases had retention of urine which persisted into the later stages of the disease. They were treated in the acute stage by catheterization twice daily and in the convalescent stage by intramuscular injections of carbachol. Two of these patients and three female patients, all of whom had been catheterized, developed urinary infections. They were treated initially with sulphadimidine, 1 g. eight-hourly. Four of them did not respond and were given chloramphenicol, 500 mg. six-hourly. Two of the females died, apparently as a direct result of their urinary infection.

There were two cases of spinal fracture, but as both patients had received injuries which could have caused the fractures, it is not possible to be certain whether these were due to or only aggravated by tetanus. One had an "operahat" fracture of T. 4–T. 10; the other had a compression fracture of L. 1. Both patients had plaster jackets applied in the convalescent period and both had a good result.

One patient died following a severe hyperpyrexial reaction to an intravenous infusion. Three patients sustained severe lacerations of the tongue through biting during spasms. In each case the tongue was almost severed. One male patient, in whom the causative injury was in the right forearm, continued to have localized spasms of the muscles of the forearm for a total of 58 days from the onset of spasms, and for 32 days after the cessation of generalized spasms (Millard, 1954).

One patient was 36 weeks pregnant at the onset of the disease. She was admitted on the seventh day, having had generalized spasms for five days. She gave birth to a live child eight hours after admission. Generalized spasms continued throughout the labour and continued until the 11th day after admission. The child was healthy and at no time showed signs of tetanus. Both mother and child were well when discharged from hospital 30 days after admission.

Observations on Fatal Cases

If we omit cases which had a known complication that may have contributed to death, and those which were treated with relaxant drugs, there remain 47 patients who died apparently as a direct result of tetanus, four of whom had periods of onset of over 48 hours. Two of these were old by Nigerian standards—48 and 55 years—and, as they died on the eighth and ninth day of the disease respectively, exhaustion and age may have been largely responsible. In the remaining 45 cases the only consistent feature is that they all had generalized reflex spasms which continued until death. All except three cases had a pyrexia at some time.

Discussion

The main source of infection in tetanus is the soil (Boyd and Maclennan, 1942; Knott and Cole, 1952). It is therefore not surprising to find that in a country like Nigeria, where the population is largely unshod, the largest single group of cases followed injury of the lower limbs. If, as is probable, the cases in which no causative injury was found followed small healed injuries of the lower limbs, then more than half (65%) of the cases are attributable to this source. Apart from acute injuries, tetanus is a serious and by no means uncommon complication of any condition, such as guinea-worm infestation (Bryant and Fairman, 1940), which causes chronic ulceration.

The only other large aetiological group is made up of cases which followed childbirth and abortion. The mortality (60%) in these cases was not much higher than that of the series as a whole, and compares favourably with the 75–100% quoted by other writers (Sahiar, 1954; Adams and Morton, 1955).

The post-operative cases show the necessity for an absolutely efficient sterilizing technique, and the remainder of the cases demonstrate well the variety of portals of entry of infection in this disease.

Shackleton (1954) has drawn attention to the necessity for taking into account prognostic criteria before assessing the value of any method of treatment in tetanus. By using the period of onset and of incubation, as described by Cole (1940) and verified experimentally by Pillemer and Wartman (1947), and a practical modification of Shackleton's (1954) classification, it is possible to divide otherwise healthy cases of tetanus into two groups—namely, mild cases, which will recover, and severe cases, in which the issue is in doubt. Cases in which the incubation period is over nine days and the period of onset over 48 hours constitute the mild ones, and in such cases it is not justifiable to use methods of treatment which are in themselves hazardous, nor is it possible to assess the effect on mortality of any method of treatment. Severe cases are those in which the incubation period is under nine days and the period of onset less than 48 hours. It is by their effect on the mortality of these cases that new methods of treatment must be judged. It is clear from the above findings that no case of tetanus must be judged hopeless on prognostic criteria alone.

The use of muscle relaxants in the treatment of tetanus, implying as it usually does long periods of artificial respiration, and requiring skilled attention, is not a practical proposition in an area where the incidence is high and trained staff scarce. It is felt, however, that mephenesin, given intravenously as described above, could be used advantageously for short intervals to give periods of rest to patients who do not respond well to the more usual form of treatment. The central depressant drugs, which were used in most of these cases, continue to be the most practical means of treatment. There is no need for artificial respiration or for continuous supervision, and in many cases the patient can drink, and occasionally eat, normally. Chlorpromazine, while it prolonged the effect of sodium amylobarbitone, seemed to have no specific effect on the disease. It is now felt, in the light of further knowledge (Godman and Adriani, 1949; Forrester, 1954; Forbes and Auld, 1955; Galloway and Wilson, 1955), that if tracheotomy had been freely carried out in cases of the severe group and the usual means of sedation employed, the nursing problems would not have been overwhelmingly increased and the mortality would probably have been reduced.

While the prophylactic administration of small doses of tetanus antiserum at the time of injury has reduced both the incidence and the mortality of tetanus (Bruce, 1920; *History of the Great War*, 1922), the results of treating established tetanus with large doses of antiserum are inconclusive (Huntington *et al.*, 1937; Bryant and Fairman, 1940). The giving of antiserum can in itself be dangerous (Bruce, 1920), and sensitivity tests are often misleading (Moynihan, 1956). In the cases here reviewed the mortality was not significantly higher in those cases which had no antiserum, nor did the severity of the disease appear to be less in cases that were given antiserum early in its course. There appears to be no justification for assuming that the prompt administration of large doses of antiserum will immediately arrest the progress of tetanus, or, indeed, have any beneficial effect.

Although the mortality in tetanus is higher in patients who have a pyrexia, this is not a constant feature in those dying from the disease. Pyrexia is probably due in every case to some degree of chest infection. The only constant feature in those dying from tetanus appears to be the presence of reflex spasms, which continue until death.

In our present state of knowledge the greatest hope of reducing the mortality from tetanus in Nigeria lies in prevention. While it is important to instruct the public how to avoid infection, the most rapid and most certain method of prophylaxis is by immunization with tetanus toxoid (Hampton, 1954; Emmett and Breck, 1955). A primary immunizing course of two injections of toxoid at an interval of six weeks, followed by a booster dose, will confer a lifelong immunity in most cases (Peterson *et al.*, 1955; Moss *et al.*, 1955). Production of tetanus toxin from a contaminated wound will further increase the immunity (Peterson *et al.*, 1955). To immunize the whole population of Nigeria against tetanus is a formidable task, but this must be the aim. The following is a suggested approach to the problem. (1) All schoolchildren be given a primary immunizing course of tetanus toxoid and at least one booster dose during their school years. As schooling has recently become compulsory, this would prove a comprehensive measure. (2) All expectant mothers be given a primary immunizing course of tetanus toxoid during pregnancy followed by a booster dose at parturition. (As a corollary to this it is suggested that all newborn children be given a protective dose of antiserum at birth.) (3) The remainder of the population be offered immunization as soon as the above groups have been dealt with. This approach is aimed at reducing the incidence of tetanus and is at present the most promising means of reducing the mortality.

Summary

A review is made of 100 consecutive adult cases of tetanus treated at University College Hospital, Ibadan.

The problem that tetanus presents in Nigeria is discussed with reference to incidence and causative injuries.

The importance is shown of assessing prognosis before deciding the method of treatment to be used and in estimating the value of different types of treatment.

The methods of treatment used, and their suitability for an area where the incidence is high, are described.

The value of antitetanic serum in the treatment of established tetanus is questioned.

Reduction of the incidence of the disease by prophylactic immunization is suggested as the most effective means of reducing the mortality.

I am indebted to Professor A. Brown and Dr. J. R. Lauckner for allowing me to treat and investigate these cases and for their advice and encouragement. I also thank all members of the medical and nursing staff of University College Hospital, Ibadan, who assisted in the care of these cases.

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MANAGEMENT OF SEVERE TETANUS

USE OF CHLORPROMAZINE IN TWO PATIENTS

BY

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Many drugs and techniques have been employed in the search for a safe and effective method of controlling the convulsions of severe tetanus. The ideal agent should abolish spasms and provide adequate sedation without respiratory depression. Chloral hydrate, bromides, paraldehyde, magnesium sulphate, morphine, pethidine, bromethol, and various barbiturates have been used, but all have defects. More recently muscular relaxant drugs have been employed with or without anaesthetic agents and artificial respiration. While their use is logical, the full regime involves many hazards and has not been shown to lower the mortality. Some of the most convincing recent series (Forbes and Auld, 1955; Veronesi, 1956) have been managed by more conservative methods.

Following reports of the experimental and clinical control of the muscular spasms of tetanus with chlorpromazine, we determined to explore its possibilities as the mainstay of sedative and anticonvulsant therapy. This drug has been shown experimentally to have properties which make it likely to be of value in tetanus. It antagonizes some central convulsant drugs (Courvoisier *et al.*, 1953); in cats it inhibits motor activity induced by cortical stimulation and suppresses the postural responses which occur on stimulation of the cerebellar cortex and the reticular formation (Dasgupta and Werner, 1955); it abolishes local tetanus in rabbits (Hougs and Andersen, 1954; Kelly and Laurence, 1956). The injection of chlorpromazine in cats has been shown to prolong the action of relaxant drugs such as *d*-tubocurarine and mephenesin (Courvoisier *et al.*, 1953); further, it has a direct paralytic effect on skeletal muscle (Burn, 1954).

These qualities, together with its better-known central effects as a tranquillizing agent and sedative and in potentiating the effect of hypnotic and analgesic drugs, suggest that its use in tetanus is rational. There are relatively few clinical reports of its use in the disease. Most of those that have appeared describe it as a useful adjunct in therapy (Adriani and Kerr, 1955; Bodman *et al.*, 1955) or discuss its use in mild and moderate cases (Cole and Robertson, 1955). Others have considered it a failure (Andersen *et al.*, 1955). In all these instances the doses used were small.

Our approach to the problem has been more in line with that of Kelly and Laurence (1956). We had previously observed the effect of chlorpromazine in four patients with mild tetanus in whom it relieved muscular

rigidity and minor spasms. It is the purpose of this paper to describe the use of the drug in two children with severe tetanus and to draw certain conclusions from this experience.

Case 1

The patient, a boy aged 14, was admitted to this hospital complaining of jaw stiffness and tightness in the chest for one day. Fifteen days earlier he had sustained a splinter wound to his right ankle. Six days before admission he had been given tetanus antitoxin and penicillin; the dose of both was uncertain. On admission he appeared anxious, trismus was evident, and there was slight rigidity of the upper abdominal muscles. Blood pressure was 135/80, pulse rate 80, and temperature 98° F. (36.7° C.). Mild tetanus was diagnosed. He was confined to bed, given a further 50,000 units of antitoxin intramuscularly, and 500,000 units of penicillin eight-hourly. Debridement of his wound was not performed. He was sedated with chlorpromazine, 50 mg. intramuscularly every six hours, combined with soluble phenobarbitone, 3 gr. (0.2 g.), intramuscularly three or four times daily as required. His symptoms were at first well controlled in this way, but within 48 hours of admission several severe spasms occurred with marked opisthotonos, a rigid abdomen, and increase in extensor tone of the lower limbs. The respiratory excursion was reduced, but laryngeal spasm and cyanosis did not occur.

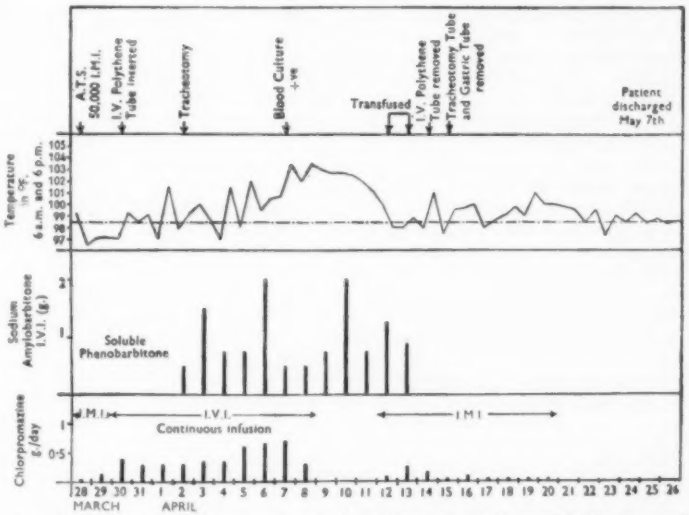
By the third day feeding by mouth was impossible, so a "polythene" catheter was introduced into the right long saphenous vein and advanced into the inferior vena cava. For the next fortnight all nutrition and drugs were administered by this route, and for three days soluble phenobarbitone, 1½ to 3 gr. (0.1 to 0.2 g.), and chlorpromazine, 50 mg., were injected intermittently into the infusion set. Control of rigidity and spasms was effective for a time, but it became clear that the effect of the drugs in these doses was transient and inadequate.

On the sixth day after admission the patient had three major spasms with respiratory embarrassment, stridor, and some cyanosis. It was then obvious that he had severe tetanus and that a more vigorous plan of treatment was necessary.

Tracheotomy was performed and a continuous intravenous infusion of chlorpromazine with supplements of sodium amylobarbitone administered. No subsequent major spasms occurred, although we observed a number of minor ones. Generally he lay with hypotonic limbs and ptosed eyelids, although varying degrees of neck and spinal rigidity and rigidity of his abdominal muscles persisted. Breathing was not depressed except when too much amylobarbitone was given; it was deep and effective, and his colour remained good.

Following tracheotomy the patient was under constant medical and nursing supervision. Careful attention was paid to nursing procedures. Every two hours he was turned, and oral, nasal, and skin hygiene and tracheotomy toilet were carried out, tracheo-bronchial secretions were carefully removed by controlled tracheal suction, and postural drainage was employed; no major pulmonary complications occurred. It was possible to maintain him in good fluid and electrolyte balance by the administration each day of 2–3 litres of fluid, containing 10% glucose and 10% alcohol, in either 0.9% saline or distilled water with daily supplements of 70–80 mEq of potassium (as 1.08% potassium chloride), 25 g. of serum albumin, and vitamins B, C, and K. His intake of about 2,200 calories daily was adequate. Full intravenous feeding was continued until he could swallow satisfactorily. A blood transfusion of 2 units of packed red cells was given on the 16th day because of an anaemia of 10 g. per 100 ml.

A blood culture taken on the 11th day, after nine days of intravenous therapy when the temperature had reached 103° F. (39.4° C.), grew *Staphylococcus pyogenes*, which was insensitive to penicillin, streptomycin, chlortetracycline, oxytetracycline, and chloramphenicol. It was sensitive only to erythromycin and novobiocin. Erythromycin was therefore given intravenously in a dose of 4 g. daily from the 11th day for one week, and thereafter by mouth. From the 13th day, 2 g. of novobiocin was given daily by intragastric tube, and later orally. These drugs were supplemented on the 15th day with intravenous penicillin, 100 million units daily, and subsequently intramuscular doses of 12–18 million units daily with 0.5 g. of probenecid. This severe septicaemia was ultimately controlled without evidence of absence formation.



Case 1. Temperature chart and record of treatment with amylobarbitone and chlorpromazine.

There were no signs of endocarditis. Antibiotics were gradually reduced and finally stopped on the 35th day in hospital. Lumbar puncture and electroencephalogram during the patient's last week in hospital were normal.

Chlorpromazine by continuous infusion and sodium amylobarbitone given as a supplement intermittently into the infusion apparatus were the sole sedative agents. The dosage and period of administration of each may be seen in the Chart. It was interesting that in the fulminating phase of the septicaemia the boy's sedative requirements fell considerably. For three days there appeared to be no manifestations of tetanus. However, as the septicaemia was controlled, rigidity and minor spasms recurred and further intramuscular chlorpromazine was required. On the 24th day, when the drug was withdrawn, all deep reflexes were increased and bilateral knee and ankle clonus were present. Spasticity and hyperreflexia in the muscles of the right leg and ankle—the region of the original wound—were especially marked. These gradually subsided by the 34th day. At this time the patient had been afebrile for five days; he was walking satisfactorily and eating well, with no trismus. There were no subsequent complications, and he was discharged 41 days after admission.

Comments.—Certain points in the administration and effect of these drugs are worth recording.—(1) Chlorpromazine was effective in relieving major spasms, although modified minor spasms were frequently observed, especially if the trachea were aspirated roughly. The patient could be catheterized without provoking a spasm. (2) Sodium amylobarbitone was necessary, but the amounts required

were small. (3) So long as the amount of amylobarbitone administered was small, there was no sign of respiratory depression, and the state of consciousness was never deep. (4) When attempts were made to reduce the dose of chlorpromazine three days after it had been started, spasms recurred. (5) Chlorpromazine diminished tracheo-bronchial secretions. (6) The drug caused no complications other than a depression and irritability which persisted for some two weeks after its cessation. There was no jaundice, and liver function tests remained normal.

Case 2

On April 7, 1957, a girl aged 12 was admitted to Tamworth Hospital, New South Wales, because she had complained of a stiff neck for four days. For three nights she had bitten her tongue in her sleep and she was unable to open her mouth. After two definite spasms the diagnosis of tetanus was made. There was no history or sign of recent injury; a possible source of infection was a dental local analgesic given four weeks previously. She was given 200,000 units of tetanus antitoxin intravenously and 100,000 units by intramuscular injection. Penicillin, 1 million units six-hourly, and streptomycin, 0.5 g. twice daily, were given.

By April 10 spasms were so severe and numerous as to cause serious respiratory embarrassment. A tracheotomy was therefore performed. Up to this point relief of spasms had been achieved with intravenous sodium thiopentone, together with pethidine, a little chlorpromazine, and soluble phenobarbitone.

The patient was transferred 280 miles by ambulance to this hospital, where she was admitted on April 11. In transit, during a severe spasm, the tracheotomy tube was ejected. On admission she was barely responsive to painful stimuli, and was rigid and cyanosed. Respiratory movements were of shallow amplitude and the respiratory rate was 28 a minute; the pulse rate was 150, and body temperature 100.2° F. (37.9° C.). She was removed to the operating theatre, where the tracheotomy tube was reinserted and an intravenous infusion begun through a polythene catheter into the right cephalic vein. For these procedures sodium thiopentone, sodium amylobarbitone, chlorpromazine, and a little succinylcholine were given. She was returned to her bed about 10 a.m., and during the next six hours received a further 0.5 g. of amylobarbitone to control two generalized spasms. Her respirations were shallow and depressed, and she became cyanosed. The untoward effect of a combination of many drugs in large doses over 24 hours was obvious. Amylobarbitone was stopped, and at 5 p.m. the administration of intravenous chlorpromazine was begun. Within two hours, after 100 mg. had been given, breathing was deeper and her colour more satisfactory; muscular relaxation was more adequate, and there was no further sign of a generalized convulsion.

From this time the patient was constantly attended by a member of the resident medical staff. Only those whose nasal swabbings were free from staphylococci were permitted to enter her room, and all wore sterile gowns and gauze masks while in attendance. Before handling any of the intravenous apparatus the medical officer scrubbed his hands in germicidal soap and donned a sterile theatre gown and sterile rubber gloves. Every two hours the patient was turned to alternate sides and pressure areas were attended to. The trachea and bronchi were aspirated regularly and a self-retaining indwelling urethral catheter was inserted.

Nutrition and drug therapy were given intravenously. The patient received each day approximately 2 litres of fluid containing 10% glucose and 10% alcohol in either 0.9% saline or distilled water, 1.08% potassium chloride, antibiotics, vitamins B and C, and 25 g. of serum albumin. No sedative or relaxant drugs other than chlorpromazine and sodium amylobarbitone were used. The former was given as a constant infusion and amylobarbitone in a 2% solution as a side drip as required.

Progress

On the day of admission *x*-ray examination confirmed the diagnosis of pneumonia in the left lower and mid-zones. Postural and percussion drainage was carried out for two weeks. "Alevaire" dispersed in carbogen was administered for 5–10 minutes hourly. By the following day the pneumonia had advanced clinically and radiologically, and the body temperature reached 102° F. (38.9° C.). Oxytetracycline, 2 g. a day intravenously, was substituted for penicillin and streptomycin. Bronchoscopy permitted the aspiration of several plugs of yellow mucopus.

By the third day in hospital very little muscular rigidity remained, and there had been no spasm since the start of the chlorpromazine infusion. Some lightening of consciousness occurred over the next 48 hours despite unchanged doses of chlorpromazine; the patient would stir in response to painful stimuli. Five days after admission all sedation was withheld for a trial period, and within three hours marked muscular rigidity and opisthotonos were obvious, although no frank spasms occurred. The injection of 50 mg. of chlorpromazine rapidly brought about a reduction of muscle tone.

On the sixth night larger doses of chlorpromazine were required and the 24-hour total reached 950 mg. The girl was restless and upset at this time, and in retrospect it appeared that a little amylobarbitone would have been more effective. Next day, the seventh since admission, a partial pulmonary collapse gave rise to laboured respiration with a sudden rise in temperature and pulse rate. Aspiration of a large lump of mucopus from the left bronchus relieved the condition. By now the girl's state of consciousness was such that she muttered coherent phrases, although she showed no tendency to spasm. This was a vivid contrast with her state on admission, when, despite barbiturate sedation to the point of respiratory depression, she was still rigid and subject to spasms.

On the eighth day slight cyanosis and distressed respiration marked a further exacerbation of atelectasis and bronchopneumonia. This improved over the next 48 hours, during which time copious secretions were aspirated from the trachea and bronchi. At this time she was transfused with 2 pints (1,140 ml.) of whole blood because her haemoglobin value had fallen to 10.1 g. per 100 ml.

By the 13th day her general condition was improved and her mental state such that she understood simple commands. Infusion of chlorpromazine, sodium amylobarbitone, and alcohol ceased at 2 p.m. Five hours later she held a short conversation with her attendants. Next morning she took fluids by mouth and breathed freely after the tracheotomy was blocked. The tube was later removed and intravenous therapy discontinued. Tetracycline, 100 mg. eight-hourly intramuscularly, was continued until 17 days after admission.

For six days after cessation of chlorpromazine she remained apathetic and took little interest in her surroundings. Her features were immobile, she spoke in monosyllables, as though with effort, and usually had to be fed. This state cleared rapidly on the seventh day and she became mentally normal. It was undoubtedly a Parkinsonian reaction such as has been described after heavy dosage with chlorpromazine. Apart from this, and a mild jaundice, she continued to improve and was fit to go home on May 11.

Successive daily doses of chlorpromazine (C.) and sodium amylobarbitone (S.A.) in mg. were:

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C.	200	500	450	350	350	950	650	625	550	450	225	150	50	0
S.A.	500	500	0	300	125	100	500	0	300	0	300	200	100	0

Comments.—The effects of chlorpromazine and sodium amylobarbitone in combination, noticed in this case, were essentially the same as in Case 1. However, mild

jaundice with a serum bilirubin level up to 3 mg. per 100 ml. developed on the 13th day of chlorpromazine therapy. This subsided quickly, and liver-function tests were normal on discharge from hospital. Bronchopneumonia was established on arrival at this hospital. This and atelectasis were the chief hazards of the illness. They were adequately controlled with antibiotics, physiotherapy, postural drainage, bronchoscopy, and regular suction of trachea and bronchi. The irritant solutions which were given through the polythene catheters caused a severe thrombophlebitis in each vein into which polythene was inserted. Peripheral veins were used in the hope of lessening the chances of septicaemia. In each case swelling and erythema subsided after four or five days.

Discussion

Both these children suffered from severe tetanus with generalized convulsions which were increasing in frequency and severity at the time when intravenous chlorpromazine was begun. In neither instance was the disease of the fulminating, rapidly progressive type which seems to make all therapeutic efforts futile. In both children respiratory embarrassment and cyanosis had become a feature of the spasms. In Case 1 the use of suxamethonium, with intermittent positive-pressure respiration, was planned, but it was rendered unnecessary by the success of the chlorpromazine–amylobarbitone regime. This led to use of the latter in the second patient, who would also probably have been managed with relaxants and artificial respiration.

Sedation

The relative ease with which the muscular spasms of these two patients could be controlled was gratifying. The combination of chlorpromazine with small quantities of sodium amylobarbitone was both simpler and more satisfactory than any drug or combination of drugs used previously in this hospital in the management of tetanus. The adequate control of violent spasms without deep anaesthesia or respiratory depression was in striking and strong contrast to the effects of drugs such as rectal bromethol or sodium thiopentone by intravenous infusion.

Previous reports have with one exception (Kelly and Laurence, 1956) described the use of, at most, moderate doses of chlorpromazine. Amounts of up to 200 mg. daily have been given. Our plan was to increase the dose so long as the drug's effect continued and there were no signs of serious sensitivity or toxicity. Accordingly these children received, for nearly two weeks, a constant infusion of chlorpromazine in amounts varying mostly between 400 and 600 mg. daily. Supplementary injections of 50 mg. were given as were required. In neither child did a major spasm occur after the drug was begun. Muscular rigidity was lessened but not abolished. In both children, but particularly in Case 1, some neck and abdominal rigidity was often present. The limbs were generally hypotonic and ptosis was evident. When the patient became rigid or a minor spasm occurred the injection of 50 mg. of chlorpromazine was rapidly effective in relieving it. There were many occasions when the children became restless, with jerky irregular breathing that was neither shallow nor depressed. These periods seldom lasted for more than a few minutes, and they appeared to be the equivalent of major spasms with the violent motor component removed. The level of consciousness was seldom deep, except when too much amylobarbitone was given in a single injection or when it was repeated too soon. These were also the only occasions when respiration was shallow and inadequate.

Tolerance to the hypnotic effects of chlorpromazine occurred in both patients. This is a common experience in psychiatric patients who take large doses of the drug. Less tolerance developed to its relaxant properties; that some did so is suggested by the increase of approximately one-third in daily dosage in both patients by the end of the first week of infusion. How far this tolerance might develop with prolonged administration is not known, but it is probable that there is a maximum effective dose beyond which any increase is futile. This raises the problem of control of convulsions in the overwhelming, rapidly progressive case of tetanus, and the extent to which chlorpromazine might be effective. It is likely that further drugs would be required for adequate control.

When chlorpromazine is employed as a sedative or tranquillizing agent it is often desirable to administer another drug because of its effect in potentiating the action of other sedatives. Sodium amylobarbitone was chosen because experience had shown it to be effective, rapid, safe, and easy to control when given in small doses. To avoid respiratory or circulatory depression it is important to give small quantities of the drug frequently rather than large doses occasionally. In these children the daily amount varied between none and 2 g. Nearly always less than 1 g. was given, and rarely was a dose of more than 200 mg. required at a time.

It was found that the balance in dosage between the two drugs was at times delicate. It was easy to give too much of one or the other. In Case 2 on one day 950 mg. of chlorpromazine was given—400 mg. during a few hours when she was particularly restless. It was without effect; but the addition of 300 mg. of amylobarbitone produced peaceful sleep, and it was clearly the drug required.

We were unable to detect any gross signs of tachycardia or fall in blood pressure or temperature attributable to chlorpromazine. No doubt they occurred to some extent, but there were no indications to suggest that such large intravenous doses should not be used. There were no signs of skin sensitivity or bone-marrow depression. In Case 2 mild jaundice developed toward the end of the second week of chlorpromazine administration, but this was transient and resolved quickly. This girl also had Parkinsonian symptoms for a week after withdrawal of the drug, and at the same time both children were in an abnormal mental state characterized by varying degrees of apathy, irritability, and depression.

Other Aspects of Management

This is no place for a full discussion of the treatment of tetanus, but some points deserve reference. During the severe phase of their illnesses these children were constantly attended by a member of the resident medical staff, which was organized into a team for this purpose. We regard this as a necessity in severe tetanus because there is no other reliable method of meeting the many sudden hazards which may occur.

While acutely ill and unable to swallow, both patients were fed entirely by vein. In the past five years nine patients with severe tetanus have died in this hospital, and at least three of these deaths were precipitated by the inhalation of gastric contents in patients fed by intragastric tube. So, apart from its effect in provoking spasms, we are averse to intragastric feeding.

Previously healthy individuals in a good state of nutrition can be adequately maintained with intravenous fluids during the critical week or fortnight of an exhausting disease like tetanus. It was possible to keep these children in satisfactory fluid and electrolyte balance for this period. The use of either 0.9% sodium chloride, or distilled water, containing 10% glucose and 10% alcohol, provided a tolerable intake of approximately 2,000 calories a day. The alcohol might have helped in sedation.

In Case 1 an almost fatal septicaemia occurred which was caused by a *Staph. pyogenes* resistant to all antibiotics in common use. Only erythromycin and novobiocin in large doses were effective in controlling it. There seems no doubt that this septicaemia originated from the polythene tube in the inferior vena cava. It resulted in a far more careful technique in all dealings with the intravenous apparatus in Case 2.

A further problem lies in the technical difficulty of infusing powerful and irritant solutions over a long period. Nevertheless, we feel that the advantages of full intravenous alimentation outweigh any shortcomings.

Summary

Two severe cases of tetanus in children are described. Large doses of chlorpromazine controlled the convulsions satisfactorily. The drug was given by a continuous intravenous infusion and was supplemented by small quantities of sodium amylobarbitone. Further relaxant or sedative agents were unnecessary. There were no serious toxic or sensitivity effects caused by chlorpromazine. Certain other points in the management of severe tetanus are discussed.

We thank Dr. A. W. Morrow and Dr. K. S. Harrison, honorary physicians in charge of these patients, for their guidance and for permission to publish this paper. We thank our colleagues on the resident medical staff and the nursing staff of the Royal Prince Alfred Hospital, in particular Sister W. Sanderson and Sister E. Parry Evans, for their care and help.

ADDENDUM.—Since this paper was submitted for publication, five patients suffering from tetanus have been admitted to this hospital. In three the disease was severe. These patients were managed according to the same plan with chlorpromazine and a barbiturate. This experience has helped to confirm the views expressed in the paper. All the patients have recovered, and we have observed no serious untoward effects from the intravenous administration of large quantities of chlorpromazine.

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A SIMPLE CYTOLOGICAL TEST FOR CANCER CURE

BY

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In the course of routine screening of vaginal smears carried out at the Cytological Laboratories of the Hammersmith Hospital during the past seven years our attention was aroused by the frequent association of malignant growth in the genital tract with highly oestrogenized smears.

Estimation of oestrogens by cytology can be done in two ways: (1) by evaluation of smear patterns—that is, taking the prevailing cell type into consideration (smears with a high oestrogenic inference show a predominance of superficial squamous cells, whereas atrophic smears are mainly composed of basal cells); and (2) by estimation of the cornification index (C.I.) (de Allende and Orias, 1950; Wachtel and Plester, 1954). The latter method, as employed by us, implies a count of 200 consecutive superficial and intermediate squamous cells and determination of the percentage of cornified cells—that is, those with pyknotic nuclei. We deliberately exclude the basal cells from this count, since they are invariably increased in the presence of infection owing to superficial erosion of the mucosa by the infecting organisms and exposure of the deeper basal layer, from which exfoliation then occurs. Cancerous growth in the genital tract is often associated with infection, and the presence of large numbers of basal cells in such cases would be wrongly interpreted as evidence of atrophy. The figures of C.I. obtained in this way are reproducible by different observers and show little individual variation (observer error).

Results

With the above technique (Wachtel, 1956) it was found that, as a rule, normal post-menopausal women had cornification indices below 10, usually below 5, provided, of course, that no oestrogens had been administered. In cases of oestrogen medication—by mouth, injection, implant, or vaginal pessary—the normal post-menopausal smear pattern changed profoundly from an atrophic to a proliferative appearance, with a simultaneous sharp rise in C.I. This sequence, with the demonstrable sharp rise in C.I. after oestrogen administration, was taken as a strong indication that the C.I. was actually a kind of yardstick for oestrogen evaluation.

Most patients with cancer in the genital tract showed high C.I.s. This finding is meaningless in premenopausal women, since naturally there are cyclical as well as individual variations in C.I. in normal premenopausal women and it would be impossible to establish what "a normal C.I. reading" should be at a given day of the menstrual cycle. Comparison of the individual figures of C.I. at ovulation time—that is, peak values—of a random sample of gynaecological out-patients attending the Hammersmith Hospital showed that the readings varied between 10 and 55. The fact that the C.I.s in pre-menopausal patients with gynaecological cancers were found to be high, but within the range of 20–60, was therefore of no statistical significance. However, of our post-menopausal cancer patients, 90% showed raised C.I.s—that is, values over 10—and the frequency of this phenomenon was regarded as significant.

The source of this excess oestrogen is obscure. For various reasons we were not sufficiently satisfied to ascribe this finding to adrenal and/or pituitary activity. Therefore, as an alternative hypothetical explanation, the assumption was made that the tumour itself might be capable of oestrogen production. Accordingly it was assumed that if this were so the C.I. would revert to low values after removal or destruction of all viable tumour tissue, whereas it would remain high if treatment had failed.

Preliminary investigations on patients with known recurrent malignant disease and on patients regarded as "cured" seemed to confirm our hypothesis (Wachtel, 1956) and encouraged us to use the C.I. as an indicator of success or failure of treatment.

In the last two years smears were taken from 165 patients at each attendance at the Gynaecological Cancer Follow-up Clinic of the Hammersmith Hospital, and the C.I., as well as the presence or absence of malignant cells in their vaginal smears, was noted. These patients were aged 24 to 80 years and had received treatment for different malignant conditions—for example, carcinoma of the vulva, Paget's disease of the vulva, squamous carcinoma of the vagina, squamous carcinoma of the cervix (all stages), adenocarcinoma of the endocervix, endometrial carcinoma, adenocarcinoma of the ovaries, cystadenocarcinoma of the ovaries, adenocarcinoma of the colon with secondaries in the ovaries, etc. The length of the follow-up period varied greatly, some having received radical treatment as long as 10 years previously and some only a few months back. Most of them, however, had been under observation for between one and two years.

Of these 165 patients, 111 showed no evidence of any clinical, histological, or cytological recurrence and had C.I. readings of under 10; while 37 had C.I. readings of over 10 and other evidence of remaining disease was found later. Nearly all these recurrences were cytologically predicted—that is, the high C.I. was the first evidence of remaining disease; in only seven cases was clinical evidence of persisting malignant growth present at the time the cytological prognosis was made. Nine patients had C.I. readings of

over 10 and no clinical evidence of recurrence at the time of writing this paper, and remain under observation; in four of these cases the observation period—that is, the time elapsed since completion of radical treatment—has not yet exceeded six months. In eight patients there was clinical and histological evidence of recurrence without rise in C.I.

Discussion

If we omit the nine cases showing high C.I. readings and no evidence of persisting or recurring neoplastic disease, because the observation period is too short to be conclusive evidence of prognostic error, it appears that a correct cytological forecast based on C.I. readings had been made in 148 out of 156 cases (94.8%). In eight (5.2%) instances the cytological prognosis based on low C.I. values was proved wrong. The 37 cases in which a correct diagnosis of persisting malignant disease was made are summarized in the accompanying Table.

It was interesting to note that, in some of the patients in whom the C.I. had remained high after full radiation treatment and histological proof of the cytologically postulated failure to respond had been obtained, subsequent surgical treatment produced a sharp drop in cornification values. These patients are presumably cured. However, in other cases the C.I. failed to drop even after additional surgery, and it is assumed that in these patients malignant disease persists. The following case histories illustrate these points.

Case 19.—Stage I cancer of the cervix was treated by two radium applications and deep *x*-ray therapy; treatment was completed in November, 1956. C.I. readings at the first follow-up attendance in December showed a C.I. of 23. Biopsy confirmed persistence of malignant disease, and Wertheim's hysterectomy was carried out on January 2, 1957. Lymph-node involvement was not detected. Subsequent C.I. estimations on three occasions were all below 10.

Case 29.—In January, 1956, cancer of the cervix was treated with full radiation doses. The C.I. was 17 in April, 27 in May, 35 in June, and 36 in July, when malignant cells also appeared in the smear. Wertheim's hysterectomy was carried out in August, and residual disease was found in the anterior lip of the cervix and lower part of the body. Post-operative C.I. estimations at monthly intervals varied between 18 and 31. A fairly hard, large mass was present in the pelvis, but it has not yet been established clinically whether this is due to fibrosis or to remaining disease.

Case 4.—Cystadenocarcinoma of both ovaries in 1949 was treated by supravaginal hysterectomy and bilateral salpingo-oophorectomy, followed by deep *x*-ray therapy. The C.I. started to rise in May, 1956, and was 32.5 in November. Subsequent biopsy of the endocervix revealed the presence of a small papillary adenocarcinoma with slight mucin secretion, the histology being identical with the lesion found in the ovaries in 1949. The patient was then treated by radiotherapy (two radium insertions). Subsequent C.I. estimations varied between 23 and 29.5. Repeat biopsies in April, 1957, showed evidence of residual tumour tissue.

Failure of Treatment Without Rise in C.I.

In eight cases secondary or residual growth was present without rise in C.I. Three of these patients were premenopausal before treatment had been given. Of the five post-menopausal women each had a low C.I. before treatment. As had been shown in our preliminary investigations, the great majority of malignant tumours, but not all, are associated with high C.I. values; it would therefore be illogical to expect high oestrogenic values after treatment in persisting disease, in the absence of high C.I.s before treatment. In order to increase the value of the test it would therefore be advisable to study pre-treatment C.I.s

Summary of 37 Cases in which Persisting Malignant Disease was Diagnosed

Case	Age	Type of Growth	Treatment	C.I. After Treatment	Result
1	63	Ca cx Stage II. Stump ca, April, 1954	DXRT	20, 7/6/55. 23, 11/10/55	Gland biopsy, March, 1956, positive, Death from ca
2	43	Ca cx Stage II, Jan., 1955	RT	28, 15/2/55	Glands in parametrium, Jan., 1956. General carcinomatosis, death
3	79	Ca ovarii, 1953	Ovariectomy, 1955. Post-op. DXRT	12, 28/2/57	Alive, but abdominal tumour present
4	50	CystadenoCa, ovarii, 1949	Subtotal hysterectomy, BSO, DXRT	32·5, 15/11/56	Recurrence in cervical stump, 27/11/56
5	66	AdenoCa colon, 1950. Ca cx Stage III, 1955	Resection, RT	12, 26/3/56	Residual growth confirmed by biopsy, 26/3/56
6		AdenoCa body and ovaries, 1950	Hysterectomy, RT	40, 8/11/56	Vault recurrence diagnosed, 1953. Slowly progressing
7	42	Ca cx Stage II, Sept., 1955	RT	14·5, 25/11/55	Clinical recurrence, March, 1956
8	52	Ca cx Stage II, Feb., 1956	RT	16, 13/5/56	Biopsy: failure to respond, July, 1956
9	51	Ca cx Stage II, Feb., 1956	RT	16, 5/4/56	Biopsy: failure to respond, 13/4/56
10	58	Ca colon, 1955	Colectomy	17, 29/3/56	D. and C. laparotomy. Recurrence in uterus and ovaries, Mary, 1956
11	71	Paget's disease of vulva	RT, 1944. Vulvectomy, 1948, 1953, 1955	10·5, 28/8/56	Extensive Paget's disease vulva and vagina, 31/8/56
12	69	CystadenoCa ovary, 1953	Pelvic clearance, RT	12, 18/10/56	Pelvic mass, 11/4/57
13	46	Ca cx Stage III, Sept., 1955	RT	14, 12/4/56	Hard mass in pelvis, 12/4/56. Death, 6/8/56
14	53	Ca cx Stage I, Oct., 1955	RT	14, 21/6/56	Biopsy: failure to respond, 21/6/56
15	50	Papillary adenoCa ovaries, Feb., 1956	Pelvic clearance, RT	12, 5/4/56	Gland secondaries, May, 1957
16	56	Ca cx Stage III, May, 1956	RT	28, 6/12/56	Spinal secondaries, 10/1/57. Death from general carcinomatosis
17	39	Ca *in situ*, 1953	Wertheim	55, 6/8/53	Recurrence in vagina, May, 1955
18	53	Ca cx Stage III, May, 1956	RT	18, 26/7/56	Recurrence in vagina, March, 1957
19	33	Ca cx Stage I, Oct., 1956	RT	23, 6/12/56	Biopsy: failure to respond, 19/12/56
20		Ca breast secondaries	RT	20, 13/3/57	Spinal secondaries
21	38	Ca cx stump, Sept., 1955	1 radium insertion, Spain 1955. Surgery England, stump and ovaries removed Aug., 1956	13·5, 4/10/56	Persisting ca
22	38	Endocervical Ca, 1955	3 × radium	35, 14/7/55	Failure to respond hysterectomy. Extensive adenoCa *in utero*, 14/10/55
23	43	Ca cx Stage I, 1953	Panhysterectomy	15, 16/7/54	Ca *in situ vaginae*, 20/7/54
24	80	Sarcoma ovaries, Nov., 1956	Ovariectomy, RT	14, 4/4/57	Hard masses in abdomen
25	48	Anaplastic Ca cx, June, 1955	Wertheim, RT	14·5, 27/1/56	Death from general carcinomatosis, 11/12/56
26	49	Ca cx Stage IV, July, 1955	Palliative, RT	19, 9/1/56	Glandular secondaries on E.U.A. exam., 9/1/56
27	48	Ca cx Stage III, Oct., 1955	RT	10·5, 9/2/56	Mass in pelvis, March, 1956. Death from general carcinomatosis, 8/10/56
28	40	Ca cx Stage III, May, 1956	RT	19, 11/10/56	Bone secondaries diagnosed, Nov., 1956
29	48	Ca cx Stage II Jan., 1956	RT	17, 20/4/56	Biopsy: Aug., 1956, failure to respond
30	57	Endometrial Ca, July, 1956	Total hysterectomy, Aug., 1956	16, 2/11/56	Secondaries in vagina
31	58	Ca ovary, secondaries omentum, April, 1956	Palliative RT partial hysterectomy	18, 28/6/56	
32	65	AdenoCa body, Sept., 1955	Pre-op. radium, 8,000 mg./hours. Wertheim	26, 23/10/55	Secondaries in vagina, March, 1956
33	42	Ca cx Stage I, Aug., 1956	RT	23, 21/12/56	Biopsy: failure to respond, 21/2/57
34	44	AdenoCa EndoCx, April, 1956	Hysterectomy, RT	19, 28/6/56	Secondaries in vagina, 13/9/56
35	49	AdenoCa body + Cx 1951. Recurrence *in utero*, July, 1955	3 × radium, 1951 DXRT, 1955	18, 22/3/56	Widespread secondaries 31/12/56
36	80	Pseudomucinous cystadenoCa ovarii, March, 1956	Palliative, RT	14, 7/6/56	Persistent growth
37	66	Ca ovarii, July, 1955	Hysterectomy–BSO	13, 8/11/55	Death from general carcinomatosis, 17/12/56

Ca = Cancer. Cx = Cervix. DXRT = Deep *x*-ray therapy. RT = Radiotherapy. BSO = Bilateral salpingo-oophorectomy.

whenever feasible. Failing this, we regard high C.I. readings after completion of radical treatment (allowing a three-months period to elapse in the evaluation of pre-menopausal cancer patients after radiotherapy) as suggestive of persistence of neoplastic disease, provided, of course, that no oestrogens had been administered. A low C.I. reading during the observation period after completion of treatment is regarded as a favourable prognostic omen only in cases in which pre-treatment C.I.s had been high.

It is not yet established whether our original hypothesis, that malignant tissue is capable of oestrogen production, is correct. In a few of our own cases urinary oestrogen estimations have been undertaken, and we are greatly indebted to Dr. Ian Ferguson Sommerville for kindly carrying out these investigations at the Endocrine Laboratories of the Institute of Obstetrics and Gynaecology in the Chelsea Hospital for Women. In the few patients investigated urinary oestrogen excretion was high and compared well with the high C.I. readings. However, these data are as yet incomplete and no conclusions can be drawn from them, although other authors (Young *et al.*, 1957) showed similar good correlation on a larger material.

The frequency with which a high C.I. reading is associated with malignant disease in the female genital tract is significant enough to suggest the use of it as a test for cure.

Summary and Conclusions

C.I. estimations in patients who had received radical treatment for malignant disease in the genital tract seemed to be of great diagnostic help in the recognition of failure of response or in the detection of early recurrence. Accurate forecasts, relying solely on C.I. readings, had been made in 94.8% of 165 cancer follow-up patients. Nine patients with a poor cytological prognosis and no clinical signs of recurrence are still under observation. The cytological prognosis was incorrect in eight patients with persistent or recurrent disease and low C.I. readings. The possible causes of this prognostic error are discussed.

The technique of C.I. estimation is easy and can be learned in a short time. We suggest that C.I. estimations should be included in routine cytological cancer follow-up investigations in view of the important implication of this test.

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"Most foundation trustees and executive officers find themselves sooner or later involved in a discussion of the relative merits of small versus large grants. Large grants, of course, are more spectacular and in a way more satisfying because of the splurge they make. Then, too, a large grant avoids the temptation of scattering the foundation's shots too widely, with the possibility of dissipating the effectiveness of its program. Small grants have in their favor, especially for the smaller foundations, the advantage of helping in areas not covered by the large grants—areas where a relatively small amount of money will make a larger project of greater value."—1956–57 Annual Report of the John and Mary R. Markle Foundation, 511, Fifth Avenue, New York, 17.

SYSTEMIC SCLERODERMA WITH PORTAL HYPERTENSION

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In systemic scleroderma ("progressive systemic sclerosis," Goetz, 1945), lesions of the hollow gastro-intestinal tract may occur at any site (Beigelman *et al.*, 1953; Cullinan, 1953; Leinwand *et al.*, 1954; Wiener, 1955; Piper and Helwig, 1955; Talbott and Ferrandis, 1956). Since, apart from one unelaborated report (Massimo, 1954), there appears to be no record of concurrent systemic scleroderma and portal hypertension, we describe here this association in two patients. Both had hepatic fibrosis, splenomegaly, and oesophageal varices with episodes of brisk haematemesis. One patient survived, following surgical relief of the effects of portal hypertension. The other, who had no operation on the portal system, died within one week of readmission to hospital for recurrent haematemesis.

Case 1

A housewife aged 31 was first admitted to St. James' Hospital for investigation in July, 1951. For two years she had felt increasing tightness of the fingers, which occasionally turned blue and cold. Although she had always been dark-skinned, pigmentation had increased in the past year. Her vitality, appetite, weight, mastication, and deglutition were all unimpaired. Menstruation was normal. The family, personal, and remote past histories were non-contributory.

Examination revealed an asthenic build (weight, 7 st. 8 lb.; 48.1 kg.), melanosis mainly sparing the face and not involving the mouth, contracture of the ocular, malar, and oral regions, and moderate sclerodactyly. The respiratory and cardiovascular systems were normal. The blood pressure was 120/85 mm. Hg. The liver and spleen were enlarged, each to about 2 cm. below the costal margin. There were no relevant neurological signs. The breasts and pubic hair appeared normal but the axillary hair was scant. No cataract, calcinosis circumscripta, telangiectasia, palmar erythema, or anterior abdominal collateral venous pattern was detected.

Investigations.—Haemoglobin level, 66% (9.8 g./100 ml.); erythrocyte count, 3,600,000/c.mm.; colour index, 0.91. The leucocyte and platelet counts were normal. The bone marrow was normoblastic. The E.S.R. was 68 mm. (Westergren) in one hour. The serum sodium, potassium, calcium, chloride, and inorganic phosphate values were normal. The blood urea was 41 mg./100 ml. Although the serum-bilirubin level was normal (0.2 mg./100 ml.), the results of other conventional hepatic tests were abnormal—that is, serum proteins, 8.75 g./100 ml. (albumin 4.15 g., globulin 4.6 g.); thymol turbidity, 15 units; and serum alkaline phosphatase, 30 K.A. units/100 ml. The 17-ketosteroid excretion was low (4.4 mg. a day). A skin biopsy showed the characteristic histology of scleroderma. The radiological findings were: chest, normal; barium swallow, incorporating the Trendelenburg position, normal;

hands and feet, absorption of the distal ends of phalanges but no calcinosis. The patient was in hospital for one month.

In November, 1951, she was readmitted and given 300 mg. of cortisone on the first day, 200 mg. on the second day, and then 100 mg. daily for two weeks, followed by a week each of 75 mg. and 50 mg. daily. Related improvement was entirely subjective—namely, increased mobility of hands and face.

In April, 1952, she was again admitted because of three episodes of haematemesis in the previous 10 hours. A fourth incident occurred a few hours later. The only fresh clinical features were undue pallor and evidence of melaena from rectal examination. The haemoglobin level remained low (6.4 g./100 ml.) after the transfusion of 3 pints (1.7 litres) of blood. Next day gastroscopy revealed two large oesophageal varices but no gastric lesion.

On the third day haematemesis recurred and operation was necessary. Through a left abdomino-thoracic incision a large adherent spleen and a fine hepatic cirrhosis were seen. There was no ascites. The portal venous pressure was 390 mm. of water. After freeing the lower 5 cm. of the oesphagus and the upper end of the stomach of all vascular connexions, subcardiac porto-azygos disconnexion by gastric transection (Tanner, 1950, 1954) was carried out. As the spleen was adherent it was removed to facilitate access to the cardiac region. A liver biopsy was not made. The splenic histology was identical with that of congestive splenomegaly. The patient was again in hospital for one month.

Follow-up.—There had been no recurrence of haematemesis. The hepatic enlargement and the results of hepatic tests were virtually unchanged, while no symptoms or signs attributable to the hepatic fibrosis had appeared. A post-operative barium swallow (September, 1953) showed no oesophageal varices or sclerodermatous involvement, while further barium studies showed no gastric, small-intestinal, or colonic abnormality. Nor was calcinosis apparent radiologically. The acroscleroderma, Raynaud phenomenon, and pigmentation showed no appreciable progression. The only fresh features were angular stomatitis and xerophthalmia. The former appeared in 1953 and did not respond to a course of riboflavine; the latter sign did not seem to be due to coexistent Sjögren's disease, since other features were lacking and the Schirmer test showed lacrimal secretion.

Case 2

A housewife aged 53 was referred to the North Middlesex Hospital in December, 1953. For eight months she had passed about six motions daily. The stools resembled aluminium paint (as in the "silver stool" sign of Thomas) (Ogilvie, 1955), and neither associated blood nor mucus had been observed. Spells of diarrhoea had occurred since her early twenties. Raynaud's phenomenon began when she was 20, while telangiectasia of the face had been present for about 10 years. In the previous 18 months she had received several short courses of iron intramuscularly for a rather persistent anaemia. Ulceration of the legs had occurred intermittently for one year. Her appetite was good and she had no dysphagia.

In January, 1954, she was admitted for investigation of diarrhoea. Examination revealed a spare build (weight, 7 st. 12 lb.; 49.4 kg.); facial pallor; numerous telangiectatic lesions of the face and one on the tongue; tightly stretched skin over the hands, wrists, malar regions, and feet; scarred finger-tips; moderate digital clubbing but no abnormality of the respiratory system; a haemic murmur and systolic hypertension (170/90); hepatic and splenic enlargement, each to about 1 cm. below the costal margin; varicose eczema, but no oedema, of the legs.

Investigations.—Haemoglobin level 67% (9.9 g./100 ml.); erythrocyte count, 3,550,000/c.mm.; colour index, 0.93. The leucocyte and platelet counts were normal. The E.S.R. was 56 mm. (Westergren) in one hour. The serum bilirubin was 1 mg./100 ml.; serum proteins, 4.7 g./100 ml. (albumin 3 g.); thymol turbidity, 6.5 units; and serum alkaline phosphatase, 81 K.A. units/100 ml. The oral glucose-tolerance test showed a "flat" curve (fasting value of 68 mg./100 ml. and successive half-hourly levels of 120, 115, 104, and 78 mg./100 ml.). Stool examination showed occult blood in each of three specimens but no organism of the *Salmonella* or *Shigella* group was isolated.

Chest *x*-ray examination showed left ventricular enlargement and clear lung fields. Barium studies disclosed loss of colonic haustrations and redundancy in the sigmoid segment as the only abnormalities. Oesophagoscopy down to the level of the gastric mucosa revealed no abnormality.

Exploratory laparotomy was undertaken to exclude a colonic neoplasm. The liver was found to be granular but not nodular. The spleen was firm and enlarged to 9 in. (23 cm.) in its long axis. A few ounces of ascitic fluid was present. The mesenteries of the small and large bowel contained haemorrhagic lymph nodes. The colon was dilated but not hypertrophied, and showed a general milky opacity and a complete loss of haustrations. The stomach, gall-bladder, small bowel, and appendix all appeared to be normal.

Biopsies of the liver and of a haemorrhagic lymph node were taken. The hepatic histology showed a distinct cirrhosis with hyperplasia and much round-cell infiltration. The lymph node revealed "sinus catarrh."

Frequently loose stools persisted. The patient was in hospital for three months.

In September, 1954, she was readmitted because of haematemesis. On admission the haemoglobin level was 3 g./100 ml., so blood transfusion was promptly begun. Pronounced shock, moderate oedema, and slight icterus were the only fresh clinical findings. After transfusion of 6 pints (3.4 litres) of blood the haemoglobin level was 5.9 g./100 ml.

The results of hepatic tests showed as the main changes a raised serum bilirubin level (2.1 mg./100 ml.) and lowered serum alkaline phosphatase (57 K.A. units/100 ml.). A barium swallow revealed a marked diminution and peristalsis, with dilatation but no constriction of the oesophagus. A barium meal with follow-through showed no gastric or duodenal lesion but many dilated coils and a few areas of constriction in the small intestine, where the mucosal pattern, especially of the jejunum, was coarse. A daily dose of 100 mg. of cortisone for two months produced no improvement in the acroscleroderma or in the colitis, and "mooning" of the face appeared. This treatment was therefore suspended for three weeks, then a daily dose of 50 mg. was given for one month. The supportive treatment was a high-calorie, high-vitamin, low-residue, low-salt diet; mistura kaolini et morphini; daily retention enemas of 0.5% tannic acid; and intramuscular injections of iron. However, on discharge from hospital after a stay of five months the only evidence of improvement was the disappearance of icterus and a haemoglobin level of 70% (10.4 g./100 ml.).

The patient was readmitted in July, 1955, on account of recurrent melaena. Her haemoglobin level had fallen to 5.5 g./100 ml., and 7 pints (4 litres) of blood was transfused. Impaired biliary excretion was revealed by intravenous cholangiogram, in which biligrafin produced no outline of the hepatic ducts or gall-blader. A fat-absorption test gave a value of only 70%, which was in keeping with the earlier demonstration of a "flat" glucose-tolerance curve. Steatorrhoea was also separately confirmed by a faecal fat value of 41.2 g./100 g. of dried stool. No special treatment was prescribed for the steatorrhoea. On discharge from hospital after a stay of 11 weeks the haemoglobin level was 60% (8.9 g./100 ml.).

The patient was again admitted in September, 1955, because of recurrent haematemesis and melaena. Icterus and oedema were minimal. There was no ascites. Her haemoglobin value was 30% (4.5 g./100 ml.), but rose to 43% after the prompt transfusion of 3 pints (1.7 litres) of blood.

Numerous investigations, some merely repetitive, were made. For convenience, only a few of these are mentioned. Blood investigation showed no L.E. cells, a negative Coombs test, and a normal red-cell osmotic fragility curve. The blood-urea level was 33 mg./100 ml. Hepatic tests showed: serum bilirubin, 2.2 mg./100 ml.; prothrombin index, even without parenteral vitamin K administration, 100%; thymol turbidity, 15 units; serum alkaline phosphatase, 70 K.A. units. The electrocardiogram was consistent with myocardial involvement. *X*-ray examination of the hands showed speckled calcinosis and distal erosion of the terminal phalanges as in the Thibierge–Weissenbach syndrome. A barium swallow revealed no oesophageal varices, but the oesophagus showed absence of peristalsis, slight general dilatation, and an irregularity of the lower end, which was interpreted as a sequel to oesophagitis, since considerable oesophageal reflux occurred in recumbency. The barium-meal pattern was still normal. During the barium enema it was observed that the colon was dilated, toneless, and almost devoid of haustrations. After evacuation, following complete colonic filling, no area of normal mucosal pattern could be demonstrated, the colonic wall appearing fluffy as in colitis. Further study of the colonic mucosa by sigmoidoscopy showed that the sigmoid segment was red and granular, and bled readily, but no discrete ulceration could be demonstrated.

On April 18, 1956, the patient was discharged with a fairly stable haemoglobin level of 60% (8.9 g./100 ml.). Despite weekly injections of iron intramuscularly the blood film still showed signs of a marked iron deficiency.

In May, 1956, the patient was admitted to the Whittington Hospital following a further haematemesis and the continued passage of loose blood-stained motions. The haemoglobin value was 20% (3 g./100 ml.) and the blood pressure 80/40 mm. Hg. Clinical improvement followed the transfusion of 5 pints (2.8 litres) of blood. Her haemoglobin level was 57% (8.4 g./100 ml.), but the blood urea had risen to 75 mg./100 ml. A few days later, icterus deepened and she lapsed into fatal coma.

Post-mortem Findings

Examination showed a waxy pale woman, 5 ft. 6 in. (167.5 cm.) in height. The skin of the hands, wrists, neck, and ankles was thickened. Many transfusion scars were seen. She had congestion of the brain and meninges, the lungs were grossly oedematous. The heart was enlarged to the left, its valves were healthy, and the coronary arteries were patent, but the myocardium was extremely pale and soft. The lower oesophagus was dilated and showed several varices. The stomach was dilated and grossly deformed by adhesions to the liver. The intestines were oedematous and, like the stomach, contained blood. The liver (weight, 1,575 g.) showed a fine cirrhosis with a smooth capsular surface and varying degrees of nodularity. The sectioned liver tissue appeared pale and bile-stained. The spleen (weight, 49.5 g.) was firm and enlarged. The gall-bladder appeared healthy and there was no cholelithiasis or other abnormality in the extrahepatic biliary tract to explain the greatly elevated alkaline phosphatase level. The generative organs and renal tract were healthy, apart from pallor of the kidneys.

Death was ascribed to melaena from oesophageal varices with hepatic cirrhosis (non-alcoholic) and scleroderma.

Histology.—A virtually complete histological study, designed to ascertain evidence of systemic sclerosis, especially in unusual sites, proved remarkably uninformative. Sections prepared from both lobes of the liver showed, with some surprise, that the degree of the basic hepatic fibrosis was neither uniform nor intense, in contrast to the marked fibrosis which usually underlies hepatic portal fibrosis with fatal oesophageal haemorrhage. Unfortunately, a detailed examination of the portal system was not undertaken in search of an extrahepatic contribution to the advanced portal hypertension. The splenic histology conformed to that of hepatolienal fibrosis (Banti's syndrome).

Discussion

There are many *a priori* reasons, mainly indirect causations, for predicting a fair incidence of hepatic fibrosis in patients with systemic scleroderma. The hepatic mesenchymal tissue would be expected to share in the polyfibrotic process of this collagen disease. Surprisingly, however, the extensive literature on scleroderma (Rothman and Walker, 1949; Leinwand *et al.*, 1954; Wiener, 1955; Talbott and Ferrandis, 1956) provides no definitive indication of the incidence and nature of associated hepatic fibrosis of the direct, the indirect, or the fortuitous type. Reliance for a preliminary impression therefore rests on the fragmentary published clinical, histological, radiological, and biochemical evidence.

Clinical and Histological

Leinwand *et al.* (1954), in a study of 150 patients with scleroderma, clearly stated that none of their 12 cases coming to necropsy showed hepatic changes, nor were there any contrary reports. Calkins and Bauer (1955) make no mention of hepatic changes in patients with scleroderma in their discussion on the protean manifestations of connective-tissue diseases. In contrast, both Weiner (1955) and Talbott and Ferrandis (1956) merely note that hepatic changes have been observed; while Cullinan (1953), in presenting his observations on 14 cases of diffuse scleroderma, considered that there were hints of involvement of other viscera such as the liver and spleen.

Sporadic accounts of hepatic involvement in systemic scleroderma have appeared in the literature. Goetz (1945) described the clinical and post-mortem observations on an emaciated middle-aged woman with visceral scleroderma. The hepatic histology showed biliary cirrhosis without any detectable abnormality of the biliary tract or pancreas. Although Gil (1951) found hepatomegaly in two out of eight patients with visceral scleroderma, both had concurrent signs of congestive cardiac failure to explain the enlargement. Beigelman *et al.* (1953) recorded five fatalities among 15 cases of diffuse scleroderma; in two of these five there was definite fibrosis histologically. However, both patients had congestive cardiac failure, confirmed at necropsy. The necropsy findings in 31 patients with progressive systemic sclerosis were described by Piper and Helwig (1955), who contended that the liver usually showed passive hyperaemia as the sole distinctive feature. However, they referred without detail to a solitary instance of portal cirrhosis and to three examples of focal hepatic necrosis. Similarly, Harvey and Bordley (1955) described areas of hepatic necrosis in a jaundiced patient with progressive scleroderma who came to necropsy. They attributed the jaundice to congestion of the liver plus anoxia from pulmonary fibrosis and pneumonia.

Radiological and Biochemical

Boyd *et al.* (1954) reviewed the radiological observations on 63 patients with generalized scleroderma, and noted that hepatic or splenic enlargement was evident in 13 out of 24 patients so investigated. They considered that this hepatomegaly might be due to congestive cardiac failure.

There is no convincing biochemical evidence of impaired hepatic function in the scant relevant literature. The evidence is confusing rather than conflicting. For clarity, it is emphasized that a selectively deranged protein metabolism is not uncommon in patients with systemic scleroderma. In this respect the results of the serum lability tests, protein fractionation, and electrophoresis indicate the appropriate quantitative and/or qualitative deviations. The common electrophoretic pattern of the serum proteins is a moderate but significant decrease in albumin and a marked increase in the gamma-globulin fraction (Walker and Benditt, 1948), whereas the total serum protein concentration is often normal. Beigelman *et al.* (1953) found hyperglobulinaemia with a reverse albumin/globulin ratio in 5 out of 10 patients. Leinwand *et al.* (1954) recorded that the results for the cephalin-cholesterol flocculation test were positive in 10 out of 12 patients and for the thymol turbidity test were

abnormal in 8 out of 13 patients. However, the bromsulphthalein excretion and the percentage of esterified serum cholesterol were normal. Since these two tests are more specific, the possibility of misinterpretation of deranged protein metabolism as evidence of liver disease rather than as an integral feature of systemic scleroderma needs no emphasis.

The hepatic fibrosis observed at operation in our first patient defies ready explanation, since there was no evidence of malnutrition, previous hepatic or biliary disease, generalized passive venous congestion, small intestinal defect, or ulcerative colitis. Though not subject to proof, it may be a direct manifestation of the viscero-sclerodermatous process. Massimo (1954) seems to have been the first clear advocate of this view. He pointed out that both the liver and the spleen are rich in mesenchymal tissue, and he claimed priority in reporting hepatosplenomegaly in association with scleroderma. In his patient, a 54-year-old woman, splenectomy was performed and a histological diagnosis of fibroadenie of Banti's type was established. This same histological pattern of what we prefer to call congestive splenomegaly was confirmed in both of our patients. By contrast, Massimo made no mention of portal hypertension, the theme of our communication. The importance of the prompt recognition of this vascular complication, which has not hitherto received special attention, is self-evident.

Eventual hepatic fibrosis is a recognized sequel to congestive hepatomegaly from cardiac and pulmonary scleroderma and might also be expected to occur in some patients with sclerodermatous haemorrhagic colitis, especially if there were concomitant steatorrhoea as exemplified in our second patient. Her "silver stool" was regarded as a product of these abnormalities. It is, however, equally admitted that the hepatic fibrosis and its complications in our two patients might be independent of the sclerodermatous process.

Finally, we suggest that the possibility of the presence of oesophageal varices, as witnessed in both our patients, should be entertained during the standard radiological studies of visceral scleroderma.

Summary

Two illustrative cases, both in women, of scleroderma and hepatic fibrosis are fully reported. In each patient the salient feature was portal hypertension, including oesophageal varices, which led to recurrent haematemesis, an aspect apparently not previously described.

The first patient survived a palliative subcardiac portoazygos disconnexion and remained well five years later, with no subsequent haematemesis. The second patient, whose illness was further complicated by a combination of sclerodermatous haemorrhagic colitis and steatorrhoea to produce the "silver stool" sign, was treated conservatively for repetitive haematemesis. After prolonged invalidism she died in coma, as a result of haemorrhage from an oesophageal varix, some 20 months after her first haematemesis.

The scant literature on hepatic fibrosis in systemic scleroderma is reviewed and the causation of such hepatic lesions is briefly discussed in relation to the observations on our two patients.

Our thanks are due to Mr. N. C. Tanner for permission to refer to the operative details in Case 1; to Mr. K. Moore for similar authority in relation to Case 2; to Dr. R. Kempthorne, Dr. N. Whittaker, and Dr. A. L. Jacobs for permission to report the clinical observations; to Dr. F. E. Camps, reader in forensic medicine, London Hospital Medical College, for his detailed necropsy report and histological sections relating to Case 2, which Dr. W. B. Purchase, H.M. Coroner, has sanctioned; to Professor C. V. Harrison for his expert comments on the histology; to the honorary editor of the *Proceedings of the Royal Society of Medicine* for permission to report the details of the second patient more fully. This case was shown at the Clinical Section, December 9, 1955, for Dr. N. Whittaker.

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GANGRENE OF THE LEGS IN DISSEMINATED LUPUS ERYTHEMATOSUS

BY

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Disseminated lupus erythematosus has been recognized as a generalized disease since Kaposi drew attention to the systemic manifestations of lupus erythematosus in 1872 and Osler's later description in 1895. The clinical syndrome of facial erythema in the classical butterfly distribution, arthritis, involvement of serous membranes, lymphadenopathy, leucopenia, and fever are now well known, but we have been unable to find a record of any case in which gangrene of the legs was due to involvement of large arteries in this disease.

Case Report

A girl aged 14 was admitted to hospital in September, 1953, having developed an erythematous, itchy eruption on the face and hands in July, and for the past month had noticed pain in the left calf on walking, severe enough to make her stop. Four days before admission she awoke to find her left foot cold and numb, becoming painful, and later swollen. There was no relevant history apart from chilblains.

On examination her temperature was 101° F. (38.3° C.) and pulse 120. There was erythema of the face and bridge of the nose in a butterfly distribution, with a shiny erythema at the bases of the finger-nails. The left foot was cold and swollen. The calf muscles were firm and tender. Femoral arterial pulses were present and equal, and both popliteal arteries were easily palpable. The dorsalis pedis and the posterior tibial arteries could not be felt on the left side. Joint sense of the left big toe was diminished and there was some loss of light touch sensation. The urine was free from albumin. The erythrocyte sedimentation rate was 82 mm. (Westergren) in one hour. Other systems were normal. The haemoglobin was 84%, colour index 1. There was a moderate leucocytosis, with 83% polymorphs. L.E. cells were present.

Cortisone orally produced much improvement, but a small area of gangrene developed at the tip of the big toe. The rest of the foot became warm and dorsalis pedis pulsation returned. A fortnight after admission she awoke with the left foot cold and numb up to the mid-calf with loss of pulses in the foot and further sensory impairment over the toes. Intra-arterial papaverine anticoagulants and a sympathetic block had some success, and, following the latter, the foot became warmer. An arteriogram demonstrated an adequate vascular supply to the foot, although there was some narrowing of the anterior tibial artery. The E.S.R. fell to 10 mm. in one hour, but changes in the temperature of the foot from day to day continued and the foot gradually became cold for longer periods. A lumbar sympathectomy performed five weeks after admission did not improve the condition. Her general condition deteriorated, gangrene spread, and amputation of the left leg was performed on December 18, 4 in. (10 cm.) below the tibial condyles.

Dissection of the amputated leg and foot showed the arteries to be occluded by recent thrombus. Small areas of necrosis were seen in skeletal muscle adjacent to the posterior tibial artery. The upper end of the peroneal artery was practically obliterated by an organized thombus and there was fibrosis in the wall of the artery.

Any attempt to lower the dose of cortisone was followed by a flare-up of the disease and it was decided to add *para*-aminobenzoic acid by mouth. Zarafonetis *et al.* (1948) had reported promising responses to this drug in disseminated lupus erythematosus, and it was given in increasing dosage up to 2 g. eight times a day and cortisone was given in doses of 25 mg. eight-hourly. There was a favourable response to this treatment and cortisone was gradually discontinued, on this occasion without untoward effect. The E.S.R. was 16 mm. in one hour; L.E. cells became absent by the 24-hour-clot method. The patient was discharged to convalescence walking with the aid of a crutch and taking *para*-aminobenzoic acid, 2 g. four times daily.

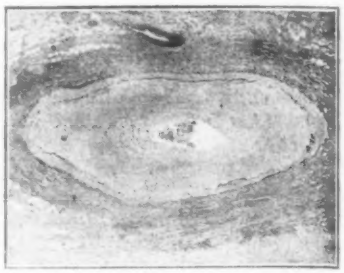
She remained well until November, 1954, when she was readmitted to hospital with polyarthritis affecting the small joints of the hands, wrists, elbows, right knee, and right ankle. A week later pain developed in the right calf followed by coldness and numbness of the right foot. The arteries below the right femoral artery were impalpable, the foot became cyanosed, and later a patch of gangrene appeared. Despite conservative treatment amputation again became necessary; but her condition deteriorated, she developed mental changes and generalized convulsions, and died eight days after operation.

Post-mortem Findings.—Internally bilateral bronchopneumonia and pulmonary congestion were found. All chambers of the heart were dilated and the myocardium was soft and pale. There were no vegetations on the valve cusps or endocardium. The left coronary artery appeared narrowed. No occluding lesion was found in the femoral or popliteal arteries other than could be accounted for by the amputations with subsequent organization. The lymph nodes were rather prominent and the spleen was congested and a little enlarged (weight 300 g.). No other abnormality was found.

Histology

Vascular lesions were found in the anterior and posterior tibial arteries of the amputated right leg, in the left coronary artery, and in many small arteries and arterioles in the liver, kidneys, skeletal muscles, appendix, ovary, connective tissues, and nerve sheaths. The left coronary artery showed perivascular fibrosis, irregular thinning of the muscle coats, and focal interruption of the internal elastic lamina with its replacement by fibrous tissue. There was a thick layer of fibrous tissue beneath the intima which had greatly narrowed the lumen of the artery. No inflammatory cells were present (see Fig.).

The anterior and posterior tibial arteries from the amputated right leg showed much narrowing of their lumina by subintimal fibrosis. There was also some recent mural thrombus, with early organization, in the anterior tibial artery; this thrombus had nearly closed the lumen. The subintimal fibrosis was not associated with destruction of the muscular and elastic tissue as it was in the left coronary artery, although there was some irregular thinning of the internal elastic lamina. Some of the venae comites contained recanalized thrombus, but the walls showed no evidence of damage.



Left coronary artery showing interruption of the internal elastic lamina, extensive subintimal fibrosis, and perivascular fibrosis. (Verhoeff's elastic stain and van Gieson. ×12.)

In the small arteries the changes consisted of perivascular fibrosis, fibrous replacement of muscle and elastic tissue for part of the circumference of the vessel, subintimal fibrosis, and occasional foci of fibrinoid necrosis in the media. In the arterioles there were hyaline thrombi with which was associated a variable amount of intimal proliferation. Histiocytes, lymphocytes, and plasma cells were present in both these types of lesion; there were few polymorphonuclear leucocytes, and eosinophils were rarely seen. A lesion of the necrotizing type was seen in an arteriole in the wall of the appendix and there was also acute suppurative appendicitis with peritonitis.

Concentric fibrosis round the splenic arterioles was present, but not to a marked extent. Wire-loop thickening of the glomerular capillaries was not seen in the kidneys. No abnormality was found in the pulmonary arteries.

Occasional small collections of large mononuclear cells, which resembled an early rheumatic lesion, were seen near many small arteries and capillaries which were not themselves abnormal. These lesions were most frequent in the muscles.

Discussion

The unusual feature of this case was the involvement of large arteries, which had caused gangrene of each leg in turn, the line of demarcation in both being typical of that produced by occlusion of the popliteal arteries. In the early stages there were probably periods of arterial spasm which was relieved temporarily by sympathetic block, and it is likely that this spasm was caused by small necrotizing lesions in the arterial walls. Later these lesions were complicated by thrombosis, and these thrombi subsequently organized. This final stage was seen in the vessels of the amputated legs. Gangrene seems to be a very rare complication of disseminated lupus erythematosus, although Raynaud's phenomenon has been reported by Dubois (1953) and Jessar *et al.* (1953).

Involvement of a main coronary artery also appears to be a rare event, although lesions in the small branches of these vessels have been described (Harvey *et al.*, 1954).

The remaining lesions in the small arteries and arterioles are as described in these vessels by Gold and Gowing (1953), and the absence of wire-loop lesions in the glomerular capillaries has been noted by many writers.

There was no evidence of active inflammation in the left coronary artery or in many of the smaller affected vessels. On the other hand, many small arteries and arterioles showed fibrinoid necrosis and active inflammation in their walls; these were plainly progressive lesions, while the former were those which had undergone organization. In between these extremes were many lesions showing intermediate stages of healing. The natural tendency of the vascular changes is to heal by organization, and it is likely that this process continues during remissions induced by cortisone therapy.

Little attention seems to have been given to the effects of cortisone treatment upon the appearance of the vascular lesions in this condition. In the present case both active and old organized foci were found at necropsy. Brunsting *et al.* (1951) stated that there was little alteration in the tissue changes following cortisone treatment. We conclude that by prolonging life it is likely that a greater proportion of organized lesions will be found at necropsy. No changes in the arteries so impressive as those found in polyarteritis nodosa after cortisone treatment by Baggenstoss *et al.* (1951) or after adrenocorticotrophic hormone by Symmers (1953) were to be seen, although the arterial lesions in the two diseases are in many ways alike, particularly when large vessels are affected.

Summary

A case of disseminated lupus erythematosus is described in which gangrene affected both legs in turn.

Widespread, active, necrotizing vascular changes were found and many similar lesions which had undergone organization. Arterial thrombosis had occurred in the legs.

The effects of systemic cortisone treatment upon the vascular changes in this disease are briefly commented upon.

We wish to thank Dr. R. A. Hickling and Dr. B. Fowler for permission to publish this case.

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CHRONIC NEPHRITIS DUE TO INGESTION OF LEAD-CONTAMINATED FLOUR

BY

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An unusually high incidence of chronic nephritis has been noted among the inhabitants of villages situated along the River Kolubara in Serbia. In an effort to find a cause for this my colleagues and I (Danilović *et al.*, 1957a, 1957b) investigated 12 families living in the village of Sopić, which seems to be the worst affected. During the last 15 years 37 members of these 12 families have died from chronic nephritis. Of the 44 members now living, 23 are suffering from nephritis, the 21 healthy members including mostly children and young adults.

The results of bacteriological investigation, including examination of throat swabs, determination of serum antistreptolysin titres, agglutination tests, and urine examination, were negative (Djurisić). The fact that a number of patients gave a history of attacks of lead colic prompted a search for a possible source of lead contamination, and the flour used in the district came under suspicion. This was ground at an ancient water-mill from corn grown by the peasants themselves. Analysis of samples of the flour showed the content of lead to be five to ten times above the safety margin (Mokranjac). When the grindstones through which the corn passed were examined they were found to contain large quantities of lead; large amounts were also present in the material used for repairing holes in the stones. Further investigation showed four to five times more lead in the flour than in the original corn. No traces of lead were found in samples of the earth in which the corn was grown, in the water, or in the containers used for storage.

Clinical and Laboratory Findings

The clinical picture in the affected cases was characteristic. Patients gave a history of a feeling of lassitude, repeated headaches, vague abdominal pains accompanied by constipation, and pains in muscles and joints. Four patients had suffered from lead colic. The blood pressure was raised in 20 cases. Signs of lead poisoning were seen in the gums in two cases. There was pallor, and in most cases haematological examination revealed a mild hypochromic anaemia with an erythrocyte count of 3–4 millions per c.mm. Two cases had punctate basophilia, the proportion of stippled cells being greater than three per thousand erythrocytes. The leucocyte count was normal. In 19 cases there was azotaemia, with a blood urea of more than 50 mg. per 100 ml. The lead content of the blood was high, amounting to 100–200 μg. per 100 ml. or more, in seven cases. Proteinuria occurred in 16 cases; the urinary content of coproporphyrin was increased in all cases. Changes in the fundus oculi were present in three cases.

Post-mortem Examination

In one case in which death in uraemic coma occurred during the course of the investigation a diagnosis of nephrosclerosis arteriosclerotica saturnina was established at necropsy, the histological picture being that of "nephrosclerovascularis of the type nephrosclerosis arteriosclerotica-nephritis saturnina (Ignjačev)." The liver was found to contain 600 μg. of lead per 100 g. of tissue, and the kidneys and spleen 320 μg. per 100 g.; in the scalp hair there was 4 mg. and in the axillary hair 10 mg. Pb per kg., as compared with a normal content of 0.2–0.6 mg. per kg.

Discussion

Our experience has shown that chronic nephritis following the continuous absorption of small quantities of lead through the alimentary tract is manifested by lassitude, headaches, abdominal pain with constipation, and pains in the muscles and joints. These are accompanied by an increase in arterial tension, a mild hypochromic anaemia, and a slight increase in blood urea (50–100 mg. per 100 ml.). A rise in the blood level of lead and an increased urinary excretion of coproporphyrin also occur and are significant findings. The disease may exist for many years in an apparently mild form, but when the blood urea rises above 100 mg. per 100 ml. the patient's condition becomes serious and death may supervene within a matter of months or at most one or two years. The disease has characteristic anatomo-pathological and histological features, and involves predominantly the cardiovascular system.

Our investigations have been extended to include other villages where the flour ground at the water-mill at Sopić is used. In our view the chronic nephritis here described is of more than local significance, and it is hoped that our continued investigations will throw further light on the pathogenesis and the clinical and anatomo-pathological features of this form of the disease.

Summary

The frequency of chronic nephritis in a Serbian village has led to an investigation of 12 affected families, 37 of whose members have died from the disease in the last 15 years. Of the 44 members now living 23 suffer from

nephritis. The primary cause of the disease was found to be the flour consumed in the district, which is heavily contaminated with lead during milling.

The clinical and laboratory findings, together with the necropsy report in a fatal case, are given.

Further investigations in other villages are being undertaken.

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Medical Memorandum

Ergot Poisoning Causing Death in Pregnancy

Search through the literature has not revealed any reported case of ergot poisoning in pregnancy causing death. Undoubtedly ergot is being taken illegally in many cases to procure abortion, and it is therefore the more surprising that such cases have not come under hospital observation.

CASE REPORT

An unmarried girl aged 20 was brought into hospital at 2 a.m. by a young man, who said he thought she was having a miscarriage. The patient, although very restless, was quite rational. She gave a history of some vaginal bleeding about 12 hours previously; her last menstrual period started 4½ months ago (equivalent to a 20-weeks pregnancy). She complained of difficulties with her breathing, which she had experienced for the last few hours, and abdominal pain for about 12 hours. In answer to a direct question she denied having interfered with her pregnancy.

On examination she was very pale, restless, and cold and clammy to touch. The pulse was not palpable at the wrist and the blood pressure could not be recorded. Her breathing was distressed and she had been incontinent of faeces. Her mucous membranes were of good colour. Per abdomen, the uterus was enlarged and the fundal height was equivalent to a pregnancy of 24 weeks. There was no apparent tenderness or other abnormality. Vaginal examination showed no evidence of bleeding, the cervix felt normal, and the os was quite closed. During the vaginal examination the patient was incontinent of faeces and urine. Over both lung fields rales and coarse rhonchi could be heard, and were so loud as mainly to obscure the heart sounds, which were about 100 beats a minute. The jugular venous pressure was not raised.

Just before 2.30 a.m. the patient had a convulsion and died. Attempts at resuscitation were of no avail.

When questioned, some time before the death of the patient, the young man was asked again if he could not give some information relevant to the girl's condition, and said that he thought she had been taking tablets of some sort. The drug ergot was not mentioned until after the girl's death.

POST-MORTEM FINDINGS

Both lungs were extremely congested and oedematous. Small, dark, firm areas were seen under the pleura, which also showed petechial haemorrhages. The heart muscle was flabby, otherwise normal. The stomach contained some vegetable matter and the small intestine some mucus. No evidence of tablets was seen. The uterus was very dark brown in colour and the muscle extremely flabby. The fundus reached to the umbilicus. The foetus was in intact membranes. There was a small clot and haemorrhagic fluid close to the placenta, anteriorly, probably the equivalent of 100 ml. of blood. From the measurements and weight of the foetus the approximate period of gestation was five months. All organs were very congested. There were ecchymoses on the abdominal side of the diaphragm.

Histology.—The uterine muscle was completely necrosed except for a narrow subserous zone of the external layer of fibres about 1 mm. wide, where some muscle fibres had survived. This zone was demarcated from the remainder of the uterine wall by a dense line of infiltration of polymorphonuclear leucocytes. The necrosed tissue showed much haemosiderin. The arteries in this area were also necrosed. No bacteria could be demonstrated by Gram stain. The sections of heart muscle, placenta, lung, kidney, and liver showed congestion only.

Analyst's Report.—Tablets found by the police, as well as stomach content and various organs, were sent for analysis to the Analytical Laboratory in Lewes, and Mr. V. C. Branson, the Deputy Public Analyst, confirmed the tablets to be prepared ergot 2½-gr. (0.16-g.) tablets. The alkaloids of ergot were present in the stomach contents, the amount being equivalent to at least five of the above tablets. Analyses of other organs were consistent with the presence of the alkaloids of ergot, together with decomposition products. Decomposition products made it impossible to estimate with any degree of accuracy the amount of ergot present, but it was of the order of 0.6 mg. in certain tissues.

COMMENT

The relatively small concealed haemorrhage may have produced some shock, but could hardly account for death. The action of some ergot alkaloids is known to produce inhibition of sympathetic nerves and vasodilatation (Dale, 1906). The dihydrogenated alkaloids of the ergotoxine group may produce hypotension, not by peripheral sympathetic blockage, but apparently by central depression of sympathetic vasomotor tone (Peters, 1956).

The histological findings of almost complete necrosis of the uterine muscle and subsequent resorption of toxic substances would add to the picture of sudden shock. All three factors together are therefore most likely to have contributed to the final catastrophe.

The dosage in this case is not known, but may have been large. More essential is the fact that the crude extract was taken, with its many alkaloids. The most disturbing feature of this case was the taking of the drug in a fairly progressed stage of pregnancy, with sequelae probably much graver than would have occurred during the first three months of gestation.

Inquiries of the girl's friend only revealed that the patient had colicky pains in her abdomen for the previous 24 hours, that she had breakfast 14 hours before death (her last meal), that she complained of being cold, and that she had to retire to bed some 12 hours before death. She was dozing in bed most of the time, but was not asleep and was twice sick. She was always rational and talked coherently.

During the inquiry it came to light with what apparent ease the drug can be procured. Midwives can get it without a doctor's prescription for post-partum haemorrhages, and veterinary surgeons often prescribe it for animals.

We wish to thank Miss M. K. Lawlor for permission to publish this case, which was admitted to hospital under her care.

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During 1957 over 4,000 became members of the Royal Society of Health. The total membership now exceeds 18,000, the highest figure ever recorded in the 81 years of the society's existence. The society's plans for this year include the building up of a permanent collection of public health exhibits in its new Health Exhibition Centre.

Reviews

CENTENARY OF "THE ORIGIN OF SPECIES"

A Hundred Years of Evolution. By G. S. Carter. (Pp. 206 +x. 21s.) London: Sidgwick and Jackson. 1957.

One hundred years ago, in October, 1857, Charles Darwin wrote a long letter to the American naturalist Asa Gray enclosing (as he put it) "the briefest abstract of my notions on the means by which Nature makes her species." This abstract is an outline of *The Origin of Species*, published in 1859. We are about to celebrate the centenary of Darwinism. The celebration will include a procession of books about evolution, and Dr. Carter's volume is one of the earliest in the procession. It is written for that variety of *Homo sapiens* to which many of us like to believe we belong: the intelligent layman. It deals with the questions which the intelligent layman is likely to ask: What was the state of thought about evolution before Darwin? What was the impact of *The Origin of Species* on Darwin's contemporaries? What modifications have been made in Darwin's theory after a century of research? Dr. Carter deals faithfully with these questions. He summarizes the familiar story of Mendel's discovery, and the comparatively recent work which has united Darwinism and Mendelism into one comprehensive theory of organic evolution.

While he is on biological ground, Dr. Carter writes accurately and with authority. But on page 5 of his book he promises to tell the reader something about the interactions between scientific thought and the intellectual world outside science. His attempts to do this are somewhat disappointing. He suggests, for example, that the cult of *Naturphilosophie* in Germany paved the way for the later development of evolutionary ideas: this suggestion would certainly be disputed by some biologists who are familiar with that strange cult. He hints at, but does not develop, the great significance of Tennyson's *In Memoriam* (published nine years before *The Origin of Species*) to any study of scientific thought in that age. He acknowledges, but does scant justice to, the influence of the Utilitarians on pre-Darwinian thought. He has only a passing reference to Nietzsche and no reference to Marx. However, this no-man's-land between science and political thought is boggy and dangerous, and if Dr. Carter had not promised to take us there we would have no grounds for disappointment; for the purely biological part of the book is a workmanlike and balanced piece of writing.

One word about the responsibility of the publisher, or rather the publisher's lack of responsibility. Out of deference to their subject, books about Darwin should be carefully produced. This book has evidently been produced in a hurry. *Naturphilosophie* is a German word. It is spelt once with a capital N and several times without, and it is given a superfluous hyphen. The word "geology" is dignified by a capital G in the middle of page 45 and a small g at the bottom of the same page. "Medicine" earns a capital M, but zoology and biology receive no capitals. Book references (essential in a work like this) are sometimes complete (p. 73), sometimes lack the publisher's name (p. 62), and sometimes lack both date and publisher's name (p. 31). It is a pity that a book which laymen will find useful, and into which Dr. Carter has put a good deal of work, should be produced so carelessly.

E. ASHBY.

IMAGINATION AND THINKING

Imagination and Thinking: A Psychological Analysis. By Peter McKellar. (Pp. 219+xi. 21s.) London: Cohen and West. 1957.

Experimental psychologists have until recently tended to neglect the study of thinking, having been mainly preoccupied with perception, intelligence, and learning. The author of this book, who is in charge of the Psychological Laboratory of Sheffield University, has been one of the few psychologists for whom this problem has had a strong attraction. He has done valuable research into hypnagogic imagery and into disorders of thinking under mescaline intoxication. Like others before him, he made the dream and the hypnagogic state his points of departure, having found a basis for his studies in Freud's researches into the dream. He distinguishes A- (autistic) thinking from R- (reality adjusted) thinking, a distinction very similar to that made by Freud, who called the former the "primary process." In the compass of this small and very readable book Dr. McKellar discusses a surprising number of important problems. He deals with various types of pathological, including psychotic, thinking; with the influence of perception on the form of thought products and its relation to their contents; with conditions of creativity; with works of art as thought products; and with scientific thinking. Socially useful thought products, such as those that make up art and science, are shown to result from interaction of A-thinking with R-thinking. The author pays tribute to the associationists, much of whose work has stood the test of time. The main value of this book for medical psychology lies in stimulating interest in one of the most important border provinces between psychology and psychiatry and in encouraging co-operation in research.

E. STENGEL.

GENERAL PRACTICE IN THE U.S.A.

The Specialties in General Practice. Edited by Russell L. Cecil, M.D., and Howard F. Conn, M.D. Second edition. (Pp. 780+xv; illustrated. £5 12s.) Philadelphia and London: W. B. Saunders Company. 1957.

This is the second edition in six years of a book designed for the American general practitioner. It consists of a series of chapters on a limited number of "specialties"—such as minor surgery, orthopaedics and fractures, rectal diseases, and ear, nose, and throat disorders—and sections on ophthalmology, paediatrics, dermatology, psychiatry, and gynaecology and obstetrics. These sections are written by 17 different specialists, and the whole presentation tends to be rather uneven and patchy, with a number of very personal points of view that are hardly acceptable universally. Each chapter opens with a short general discussion of the subject, and there is a good deal of common sense in this part of the work. There follow more detailed descriptions of diagnosis and treatment of specific conditions considered suitable to be treated by the general practitioner. The great majority of these would not come within the province of the British family doctor—such as the treatment of major fractures, rectal operations, and various urological procedures.

A number of criticisms can be levelled at this work. Although this is a 1957 edition the majority of the references are pre-1951, when the last edition appeared, and there has been little attempt to bring it up to date. A number of references go back to the pre-war era. Some of the opinions also appear rather out of date, such as, "Myringotomy must often be performed." The diagrams showing suitable incisions for treating infections of the hand go back to the pre-antibiotic days and are quite unnecessary in the present era.

This book may be acceptable to, and suitable for, the American G.P., but it is not really of much value to the British family doctor. In the U.S.A. the general practitioner has fewer patients, who are often of the "floating" type with little permanent loyalty to any one doctor, seeking advice from different practitioners depending on the afflicting disease. With the present customs the American practitioner is expected by the patient to undertake a wider range of treatment, involving various of the more major surgical procedures, radiological examinations, and electrocardiography. Whether this is a good system or not is a matter of opinion, but at least it explains the setting and contents of this well-produced but rather expensive book.

JOHN FRY.

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PROPHYLAXIS OF RHEUMATIC FEVER

To those who are beginning to regard rheumatic fever as a thing almost of the past—a disease that is seen but rarely, and then in a mild form—it comes as something of a shock to be reminded that there are probably several thousand new cases in England and Wales every year. In 1956 there were 208 deaths directly attributable to rheumatic fever, and in the same year, and mostly in persons under 35 years of age, there were 8,208 deaths from chronic rheumatic heart disease. The recently issued report[1] of the Rheumatic Fever Committee of the Royal College of Physicians starts by making these points and proceeds to make two more. These are, first, that acute rheumatism and its recurrences are the result of infection with the beta-haemolytic streptococcus of Lancefield group A, and, second, that recurrences can be averted by preventive treatment with penicillin or sulphonamides. The acceptance of these points leads the committee to recommend that anyone who has had rheumatic fever should be given penicillin for five years or until leaving school, whichever is the longer. The report also recommends that preventive treatment should be given to any person who has had rheumatic fever and who subsequently enters a hospital or any semi-closed community such as a camp or institution. Any streptococcal infection in a former rheumatic-fever patient should immediately be treated with bactericidal doses of penicillin, and this treatment, in the committee's opinion, is justifiable in any patient whenever a presumptive diagnosis of infection with beta-haemolytic streptococci is made. Chorea is accepted as a symptom of rheumatic fever, but the report leaves it uncertain whether preventive treatment on the same lines should be given to a child who has suffered an uncomplicated attack of chorea.

These recommendations have come about as a result of the evidence that has accumulated year by year of the value of penicillin as a preventive against streptococcal infection. This has been largely transatlantic in origin and is for the most part the outcome of experiences in the Services and other semi-closed communities. E. G. L. Bywaters and his co-workers[2] from Taplow have previously strongly advocated the use of preventive therapy in rheumatic fever, on the basis of their own considerable experience as well as of the reports in the literature. They also examined the reasons why the idea of prevention had in general failed to be accepted by doctors and their patients in Britain, and it may be useful to review some of these now that the carefully weighed judgment of this report has been added in support of continuous penicillin treatment. On the patients' side, Bywaters found that parental apathy and lack of supervision militated against success. It should certainly be possible to overcome this apathy given enthusiastic encouragement from the general practitioner and perhaps some appropriate assistance from the lay press. But to suggest that lack of parental supervision is a chief cause of failure to take the penicillin regularly would be unfair, for it is very difficult to ensure that children will take a medicine regularly for a matter of years when there is no obvious ill effect from its occasional or even prolonged omission. This difficulty can be overcome by giving monthly injections of a long-acting penicillin, but the local discomfort caused by these injections is a serious disadvantage when they are used over a long period.

Bywaters found that opposition on the part of the general practitioner stemmed from a number of factors, three at least of which are very real and frequently met. These are the fear of making children hypochondriacs, lack of knowledge of the value of preventive therapy in rheumatism, and the fact that the disease is now so uncommon. Bywaters reasonably comments that hypochondriacs are made not by pills but by the attitude of the parents; but insistence by doctors in the past on the need for very prolonged limitation of physical effort after rheumatic heart disease often caused much parental anxiety which was passed on to the children, and it is possible that prolonged drug therapy might have the same effect. This is, however, not a great price to pay if severe cardiac damage from recurrences is effectively prevented. Wide dissemination of the facts brought out in the committee's report should do much to answer the other two objections. Unless there is wholehearted and enthusiastic acceptance by the family doctor, any scheme for such prolonged treatment as this is bound to fail: it requires persistence on his part and constant encouragement to the parents to continue, over many

[1] Further Report of the Rheumatic Fever Committee of the Royal College of Physicians, 1957. London.
[2] Bywaters, E. G. L., Hallidie-Smith, K., and Thomas, G. T., *Brit. med. J.*, 1957, 1, 1234.
[3] Breese, B. B., and Disney, F. A., *J. Pediat.*, 1957, 51, 157.
[4] Markowitz, M., Ferencz, C., and Bonet, A., *Pediatrics*, 1957, 19, 201.

years, a form of treatment which is much less dramatic or obvious in its results than is, for instance, the treatment of epilepsy or diabetes. The daily cost of treatment for each child is only a matter of a few pence, and even the total sum expended by the Health Service in this way is likely to be small in comparison with the saving effected by not having to treat many patients with recurrences of acute rheumatism—leaving out of account the final cost to the nation due to the disabilities from cardiac damage in later life.

As to the type of drug and dosage, the Committee's report suggests the use of penicillin (crystalline penicillin G tablets), 200,000 units twice daily, or phenoxymethyl penicillin (penicillin V), 120 mg. twice daily. Alternatively, if oral treatment cannot be given, a monthly intramuscular injection of 1.5 mega units (5 ml.) of benzathine penicillin should be given for a period. This is in line with recent American work,[3] although M. Markowitz and his colleagues,[4] who used 600,000 units of benzathine penicillin G, have cast doubt on the duration of effective prophylaxis of a single injection. They state that protection may not be afforded for more than a short time against infection with a virulent streptococcus—an observation which would tend to undermine confidence in the value of preventive penicillin therapy if it was thought that its advocates claimed it to be completely effective in every case. But no one claims that preventive treatment is invariably successful. Though streptococcal infections can occur during treatment, it is rightly claimed that the preventive administration of penicillin greatly reduces their incidence, and the liability to recurrences of rheumatic fever thus becomes much less. For successful prophylaxis it is essential that treatment be carried out conscientiously and without even occasional lapses. If this is done, we may look forward to a further fall in the number of deaths from chronic rheumatic heart disease in young people, and in addition the incidence of acute rheumatic fever will itself be diminished if all suspected cases of acute streptococcal infection are treated early and energetically with penicillin.

TRANSMISSION OF MENTAL DEFECT

In discussing the problem of whether or not subjects deemed to be mentally defective should be discouraged, or prevented, from having children, the critical information is found by studying the actual children of such people. It is popularly supposed that the mentally deficient are exceptionally prolific and that they invariably have defective offspring. In view of the importance of the question it is remarkable how few accurate data are available. One reason for this is uncertainty about the diagnosis of mental deficiency, a term which can cover gross idiocy as well as behaviour disorder in a person of almost average scholastic attainments. One way out of the difficulty is to base diagnosis on mental measurement, though even here there is no agreement about the tests to be used. Differences between verbal and non-verbal abilities can be wide, so that a person may be judged abnormal by one test and not by another. Moreover, few tests are accurately standardized for adult populations. But, at the worst, it is better to have some objective measurement than to rely upon clinical instinct, or, as some people would say, prejudice, in making the diagnosis of high-grade defect.

There are two obvious ways of tracing the children of mentally defective parents. One is to follow up and examine the offspring of pupils from special schools; the other is to study the offspring of certified, institutional cases. The two populations are different in that the educationally subnormal will tend to be of higher mental grade and less likely to be emotionally unstable than the institutional cases. The fertility of the patients can be judged by the number of offspring found, and the intelligence level of their children can be recorded.

The early surveys, like those made by H. H. Goddard[1] and E. J. Lidbetter,[2] used social criteria for diagnosis of mental defect, and they conveyed a gloomy impression. An *ad hoc* inquiry, carried out by the Brock Sterilization Committee in 1934, recorded that, among 3,650 children of mentally defective mothers, 24.8% were judged to be similarly defective, though another 18.4% were retarded. These figures can be compared with German estimates, cited by T. Kemp,[3] which suggest that one-third or more of the children of a defective subject are likely to be of similar mental grade. To fill in the picture we need to know how many children are produced by such mothers, and some information on this point has been given by T. Ferguson and A. W. Kerr.[4] A study was made of 207 young women six years after leaving Glasgow special schools: 55 had married, and this showed that the marriage rate of this group was lower than that for the population generally. Only 12 had illegitimate children. These findings agree with those of F. Visser,[5] who followed up 194 defectives in Utrecht over a much longer

[1] Goddard, H. H., *Feeble-mindedness, its Causes and Consequences*, 1914, New York.
[2] Lidbetter, E. J., *Heredity and the Social Problem Group*, 1933, **1**, London.
[3] Kemp, T., *Genetics and Disease*, 1951, Edinburgh.
[4] Ferguson, T., and Kerr, A. W., *Glasg. med. J.*, 1955, **36**, 50.
[5] Visser, F., *Mensch. en Maatsch.*, 1936, **12**, 416.
[6] Ainsworth, H. M., Wagner, E. A., and Strauss, A. A., *Amer. J. ment. Defic.*, 1945, **49**, 277.
[7] Brandon, M. W. G., *J. ment. Sci.*, 1957, **103**, 710.

period and compared them with a control group of 160 people who had been to ordinary schools. The defectives were only half as frequently married as the normals, but the number of children per family was the same in both groups.

The follow-up of patients actually certified mentally defective can be more exact by reason of better opportunities for testing. H. M. Ainsworth and colleagues,[6] for example, tested 15 children of 12 mothers; the children had a mean intelligence quotient of 91, whereas the mothers' averaged only 66. A new survey of a similar type, but on a larger scale, has been carried out by M. W. G. Brandon[7] at the Fountain Hospital. It covers 73 mothers who had previously been patients; they were admitted, on the average, when 22 years old, and followed up after periods of 10 to 20 years. The mean I.Q. of 70 of these women who were tested was 73.5: they tended to score lower on Binet-type tests than on others, and the I.Q.s had to be compounded from more than one rating. Altogether 150 offspring were produced; 108 of these had been examined, and 74 were given standardized mental tests. The mean estimated I.Q. of the group was 91.2. There had been a very high mortality rate, 41 out of the 150 having died before the time of making the investigation; among these were four cases of gross physical abnormality such as anencephaly and microcephaly. The surviving group included three imbeciles, seven feebleminded or backward children, and eight others considered earlier to be mentally defective but since discharged. As previous observers have found, there was no obvious relationship between the I.Q. of the defective mother and that of the child. The mother of the child with the highest I.Q. of 132 was herself rated as having an I.Q. of 55.

While the general result resembles that obtained by Ainsworth and his colleagues, it disagrees with those from some earlier studies. A suggestion to account for this is that, in other types of survey, the low mentality of the child is often a selective factor in bringing the mother's mentality to the notice of the authorities. Furthermore, the results obtained by using standardized psychological tests are likely to be more reliable than those obtained by social rating. Much more work needs to be done on the lines of Brandon's study. In order to obtain a complete picture, the patients' husbands also need to be tested. The mothers could be screened for known hereditary traits, such as recessive defects, and all their children classified, physically and mentally, whether or not they were surviving at the time of the survey. Without such records much information of genetical significance is likely to be missed.

ACUTE NEPHRITIS

The value of renal biopsy in the study of renal disease[1] is apparent from papers which have appeared correlating structure and function in eclampsia,[2] disseminated lupus erythematosus,[3] tubular necrosis,[4] and the nephrotic syndrome.[5] Recently two reports have appeared on renal biopsies performed in cases of acute nephritis. R. C. Bates and colleagues[6] report their findings in an outbreak of acute nephritis affecting ten patients at a naval recruit centre. All but one of the patients had also had pharyngitis, but in only one case was there any serological evidence of a recent streptococcal infection. In all the cases there was an interval of less than six days between the infection and the onset of nephritic symptoms, and in two cases haematuria preceded the pharyngitis. Gross haematuria was present in seven of the ten patients and was the outstanding clinical feature; oedema, hypertension, and impairment of renal function were uncommon. Biopsy material was obtained from five of the patients within thirty days of the onset, from two of these within ten days. The most significant histological feature in these five cases was the lack of glomerular hypercellularity or inflammatory-cell infiltration. The only abnormalities were the presence of occasional red blood cells and protein precipitate in the capsular space of some glomeruli, and a few red cells in the lumen of the tubules. In two other cases with the same clinical features, specimens obtained at biopsy 38 and 77 days after the onset showed slight focal hypercellularity of most of the glomeruli. Serum complement levels were low in all these patients, but despite virus studies no aetiological agent was found to account for the pharyngitis.

In a recent communication M. S. R. Hutt, J. L. Pinniger, and H. de Wardener[7] report renal biopsy findings in fourteen cases of acute glomerular nephritis. Nine of these cases showed the classical features of proteinuria, haematuria, hypertension, cardiac failure, and oedema occurring two to three weeks after an acute upper respiratory infection, and in three cases type-12 streptococci were isolated from throat cultures. The biopsies were performed on an average nine days after the onset of symptoms. In contrast to the cases described by Bates and colleagues all the glomerular tissue showed proliferation of tuft nuclei, increase of internuclear material, with splitting of the basement membrane, and a striking infiltration of the glomerular tuft with neutrophil polymorphs and occasional eosinophils. In six patients areas of focal tubular necrosis, with interstitial oedema and inflammatory cell infiltration, were also present. Three patients showed a different clinical

[1] *Brit. med. J.*, 1954, **2**, 1468.
[2] Pollak, V. E., Pirani, C. L., Kark, R. M., Muehrcke, R. C., Freda, V. C., and Nettles, J. B., *Lancet*, 1956, **2**, 59.
[3] Muehrcke, R. C., Kark, R. M., Pirani, C. L., Pollak, V. E., and Steck, I. E., *Ann. rheum. Dis.*, 1955, **14**, 171.
[4] Brun, C., and Munck, O., *Lancet*, 1957, **1**, 603.
[5] Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollak, V. E., *Proc. roy. Soc. Med.*, 1956, **49**, 327.
[6] Bates, R. C., Jennings, R. B., and Earle, D. P., *Amer. J. Med.*, 1957, **23**, 510.
[7] Hutt, M. S. R., Pinniger, J. L., and De Wardener, H., *Excerpta Medica, 3rd International Congress of Clinical Pathology*, 1957, 46.
[8] Sharpey-Schafer, E. P., *Lancet*, 1955, **2**, 841.
[9] Volhard, F., and Fahr, T., *Die Brightsche Nierenkrankheit*, 1914, Berlin.
[10] Bell, E. T., *Renal Diseases*, 1950, Lea & Febiger, Philadelphia.

picture, characterized by a sudden onset of oedema and cardiac failure ten days after an acute upper respiratory infection. None of these patients had proteinuria or haematuria. Serological tests for recent streptococcal infection were not performed. Renal biopsies showed only minimal changes in the epithelium of Bowman's capsule, with some protein precipitate in the capsular spaces.

The observations of Hutt and his colleagues confirm that the histological picture in acute glomerular nephritis due to a specific serological type of streptococcus is that of an acute generalized glomerular inflammation. Although the clinical evidence suggests that their three cases without proteinuria may be classified as acute nephritis,[8] the histological findings in the glomeruli were slight. The cases of Bates and his colleagues which clinically resemble those described as acute focal[9] or acute haemorrhagic nephritis,[10] also showed minimal glomerular lesions. Serological evidence suggests they were not of streptococcal origin, though the low serum complement indicates that an antigen–antibody reaction had occurred. Evidently the term acute nephritis covers a variety of clinical and histological conditions. The diversity probably results from differences in the aetiological agent and in the response of the host. Further studies of the type described here, in which clinical, bacteriological, serological, and histological techniques are combined, are necessary before a classification of these syndromes is possible.

BAGDAD TREATMENT OF BURNS

Because of the dry climate of Iraq an unusual and successful method of treating burns has been evolved by Professor W. E. M. Wardill and Dr. Khalid Naji, working at the Royal Hospital, Bagdad. They described what they had achieved by this method to the Section of Surgery at the Annual Meeting of the B.M.A. in Newcastle last summer. Paraffin stoves are commonly used in Iraq for cooking, and accidents with these often cause extensive burns, especially of women and children. There is no special accommodation in Bagdad for burned patients; they are treated in general surgical wards of the Royal Hospital. The basis of the method of treatment is to expose the burned surfaces to the air. As soon as the patient is fit, he is placed in a warm bath containing cetrimide, and this bath is repeated every two or three days. The patient is encouraged to walk to and from the bath, since early ambulation is regarded as an important part of the treatment. At the first bathing loose epidermis and blisters are excised and on later occasions raised portions of eschar or crust are removed. The resulting granulating surfaces of deep burns are again exposed and bathed at intervals. Exposed granulations remain flat and smooth and with little infection, so that exudation and secondary crusting are minimal. With no septic absorption from the burn, pyrexia is unusual and the patient's appetite and nutritional state remain good. Few bacteriological studies have been carried out, but coagulase-negative staphylococci, proteus, and *Bacillus subtilis* have been the only organisms grown from the exposed granulations. Antibiotics are not used as a routine, since it has been found that they do not alter the course of healing. Over four hundred burned patients have been treated by this method in Bagdad in the last five years. During this time skin grafting has rarely been performed: extensive deep burns have healed spontaneously, though admittedly slowly, with little contracture. The flat granulating surface facilitates inward spread of epithelium from the periphery. Islets of epithelium appear here and there in the wound many weeks after injury. Biopsies from the centres of large granulating areas have shown viable sweat glands on histological examination. It would seem, therefore, that in burns which appear macroscopically to have destroyed the entire skin thickness epithelial elements may survive in sufficient concentration to contribute substantially by their proliferation to the healing of the raw surface, if infection is avoided.

This method of treating burns undoubtedly merits more detailed investigation, but it probably has little direct application to the treatment of burns in Britain. The most significant feature, and the most enviable one to the Western observer, is the freedom from infection. This is probably related more to environmental conditions than technique. During most of the year the ward temperature in the Royal Hospital at Bagdad is between 80 and 90° F. (32 and 37.5° C.) and the relative humidity between 20% and 30%. It is likely that the low humidity and the bright sunlight are the main bacteriostatic factors. After a recent visit to Bagdad by Professor C. A. Wells and one of his associates it has been proposed that an experimental burns unit should be set up in Liverpool and the treatment of burns investigated in an environment reproducing so far as possible the climatic conditions of Bagdad.

TOWN-DWELLING, SMOKING, AND CANCER

The indefatigable Dr. Percy Stocks has taken us another step further in the search for the causes of lung cancer. Two years ago he showed[1] that mortality from this cause in parts of the north-west of England and Wales was independently related to degree of urbanization as well as to smoking habits. Though people on the average smoke more in the town than the country, the difference is not sufficient to account for the urban excess of mortality due to lung cancer. But it was rightly suggested[2] that for a full understanding of the problem we need to know something of the smoking habits of twenty to thirty years ago rather than those of to-day. Dr. Stocks, working with the Cheshire and North Wales Branch of the British Empire Cancer Campaign, has set out to fill this gap by obtaining smoking histories from 600 men in their fifties. In a preliminary communication, published in the current report[3] of the Campaign, he concludes that the ratio of cigarette consumption between the town and the country has not changed appreciably over the last twenty years. In 1952 the volume of

[1] Stocks, P., and Campbell, J. M., *Brit. med. J.*, 1955, **2**, 923.
[2] Hill, A. B., and Doll, R., *ibid.*, 1956, **1**, 1160.
[3] Stocks, P., *Annual Report of Brit. Emp. Cancer Campgn.*, 1957, **34**, 516.
[4] *Brit. med. J.*, 1956, **2**, 1535.

cigarette smoking (as defined) was 25% higher in Liverpool than in North Wales, the corresponding figure being 22% in 1932. Such figures, taken in conjunction with the earlier findings, clearly give no support to the hypothesis that it is the excess smoking of 20 years ago that now causes people to die of lung cancer more often in Liverpool than in the country. But we shall have to wait until the full results are published before we can see exactly how much reliance can be placed on these figures. It is notoriously difficult to get good information of current smoking habits; to discover how many cigarettes a week a man smoked in 1932 might well be thought impossible. However, few people know this better than Dr. Stocks, and we may assume that these results are, within broad limits, reliable. In the same report Dr. Stocks has tied up another loose end from his previous paper. He has shown that for women as well as for men mortality from lung cancer is related independently to smoking and living in towns. The estimated death rates (standardized for age) of women non-smokers varied from 87 per million in the Isle of Man to 171 per million in the Merseyside, the corresponding figures for women smokers being 186 and 757.

This work emphasizes the importance, stressed before in these columns,[4] of the regional approach to the epidemiology of cancer. It is only on this level that there are enough cases to enable valid conclusions to be drawn, while preserving the local atmosphere which is a prerequisite for a machinery entailing the use of hospital and general-practitioner records, health visitors, and the like. The British Empire Cancer Campaign, and Dr. Stocks, deserve congratulations for their pioneering activities in this field.

HOT GENES

It is not only cool heads we shall need if the human race is to continue surviving with unimpaired vigour. For according to a group of Swedish workers the wearing of clothes may raise the testicular temperature sufficiently to increase the rate of harmful mutations.[1] These workers investigated, by means of thermocouples attached to the scrotum, the effect of normal clothing on the scrotal temperature of men aged 20–40. They obtained data from clothed and unclothed men and from seasoned nudists, and found that the average scrotal temperature differed between clothed and unclothed subjects by 3.3° C. (S.E. 0.39° C.). After the men put on or took off their clothes the scrotal temperature was found to take 1–2 hours to reach a constant value. The numbers taking part in the experiment were small, so that, despite the statistically significant difference between the temperatures, the authors showed due caution in describing their work as "exploratory." To men living south of the Border it certainly explores an important subject, for the kilt would seem to offer a eugenic coolness that trousers lack. Indeed, the Swedish authors draw attention to the merits not only of this contemporary garment but also of the codpiece, now a somewhat outmoded fashion.

The exterior situation of the mammalian testicles may have resulted in a more favourable mutation rate, because as an organism increases in complexity the more likely is it that any mutation will be harmful to the propagation of its species. But much further work seems to be needed on whether the testicles, as distinct from the scrotum, of warm-blooded creatures have their temperature appreciably increased when their owner wears clothes, works in a boiler-room, or lives in the tropics. If the temperature can be harmfully raised in this way, then it seems possible that the continuous warmth provided by clothes would do more damage than, for example, the occasional warmth of a hot bath, on the assumption that the effect on the mutation rate would be a product of rise in temperature and time of exposure to it. The conclusion that a rise in temperature, if it occurs in this way, would increase the mutation rate seems plausible. It is derived by analogy from experiments on *Drosophila*, to which the Swedish authors refer, but here again further work on warm-blooded animals would be welcome. Finally, the study of mutation rates in human populations, now only in its early stages, may, if related to clothing and climate, eventually provide data of interest.

THE PUBLIC HEALTH

The Englishman's traditional preoccupation with the weather in these stormy islands surely springs from the realization that it often affects his health. Commenting on this in the Ministry of Health's report for 1956,[1] the Chief Medical Officer, Sir John Charles, reports that applications to the Emergency Bed Service are related to daily temperature; they rise just after a cold spell and fall again when the weather becomes milder. Apart from cold, fog is well known to increase morbidity in Britain, and the fog which occurred in London during January 4–7, 1956, was followed by a rise of nearly a thousand over the general level of deaths between January 7 and 14. The summer in that year was "colder and wetter and duller" than any since 1880, and in conclusion fog covered the country from December 19 to 23. But despite the coughs and shivers most of the national indices of health continued to be satisfactory. The infant mortality rate reached the record low level of 23.7 per 1,000 live births, and the 327 deaths attributed to pregnancy and childbirth were also the lowest total ever recorded. The general death rate remained stationary at 11.7 per 1,000 population.

A welcome departure from previous practice is the report's chapter on "The Cancers," so headed in the plural instead of the singular "Cancer." This is to mark the growing idea of "cancers as a group of diseases with a common link rather than of cancer as a single disease with a variety of manifestations." Preventive action has in the past been taken against certain industrial cancers, such as scrotal cancers of chimney-sweeps, bladder cancers of chemical workers,

[1] Ehrenberg, L., Von Ehrenstein, G., and Hedgran, A., *Nature*, 1957, **180**, 1431.

[1] *Report of Ministry of Health for the Year Ended December 31, 1956*, Part 2. H.M.S.O., 1957.

and bone cancers of luminous-paint workers. It is more difficult, says the report, when it "involves difficult decisions, as in the lung cancers." And "we are still left with the majority of cancers for which no exogenous cause has been suggested." Even so, a comparison with the attack on infectious diseases in the last hundred years suggests that "in far less than the next hundred years" we may succeed in elucidating many more of the cancers.

NEW YEAR HONOURS

Sir Harry Platt's term of office as President of the Royal College of Surgeons was a notably successful one, and the conferment on him of a baronetcy in the New Year Honours is a tribute to him, to the College over which he presided, and to the specialty of orthopaedic surgery for which he has done so much. Sir Harry, who was knighted in 1948, is emeritus professor of orthopaedic surgery at the University of Manchester and consulting orthopaedic surgeon to the Manchester Royal Infirmary. Sir Stewart Duke-Elder, surgeon-oculist to the Queen, director of research at the Institute of Ophthalmology, and ophthalmic surgeon to St. George's and Moorfields Hospitals, has been promoted to G.C.V.O. After a brilliant academic career, Sir Stewart quickly made an international reputation as a research worker and as an ophthalmic surgeon, and he was knighted in 1933. This latest honour is but one of many he has received, not only in Britain but in countries all over the world. The Medical Director-General of the Navy, Surgeon Vice-Admiral Robert Cyril May, is appointed K.B.E. Having served as a combatant in the Army in the first world war, he entered the Navy in 1925 after qualifying as a doctor at Guy's Hospital, and became a surgical specialist. He has also had a very wide experience of medical administration, having been assistant to the Medical Director-General during the second world war. The Director-General of Medical Services, Royal Air Force, Air Marshal P. B. Lee Potter, is also appointed K.B.E. Graduating from Sheffield University in 1928, Air Marshal Lee Potter had been principal medical officer of Bomber Command and director of hygiene and research at the Air Ministry before he was made Director-General a year ago.

The public health service in particular will be delighted that Dr. Kenneth Cowan, Chief Medical Officer of the Department of Health for Scotland, has received the honour of knighthood. An Ulsterman, Dr. Cowan was county medical officer of Gloucestershire and of Essex before he succeeded Sir Andrew Davidson in Edinburgh three years ago. From 1952 to 1954 he was chairman of the Public Health Committee of the British Medical Association, and his able conduct of the business of the committee was of the greatest service to the Association during a particularly difficult period. Professor Hans Adolf Krebs, Whitley Professor of Biochemistry at the University of Oxford, also becomes a Knight Bachelor. One of the most distinguished medical research workers in Britain, Professor Krebs shared the Nobel Prize for Medicine in 1953 for his discovery of the citric acid cycle in the metabolism of carbohydrates—the Krebs cycle. He came to this country from Freiburg in 1933. During the war he did invaluable work on vitamin deficiencies at Sheffield and was appointed professor of biochemistry there in 1945. Professor Krebs, who was elected F.R.S. in 1947, has been at Oxford since 1954.

The well-known London coroner, Dr. William Bentley Purchase, is another medical man who receives the honour of knighthood. Called to the Bar in 1919, in the same year as he graduated in medicine at Cambridge, Dr. Bentley Purchase practised as a barrister for several years before being appointed one of the coroners for the county of London in 1930. Since then he has become known to a wide public, and is greatly respected for the exemplary way in which he conducts the business of his court and for his profound knowledge of coroner's law. He has been coroner to the Queen's Household since 1955.

Three well-known medical men in Australia have been made Knights Bachelor. Mr. W. G. D. Upjohn, consulting surgeon to the Royal Melbourne Hospital and the Children's Hospital, Melbourne, is a former president of the Victorian Branch of the B.M.A. He has held many teaching posts in the University of Melbourne, and is the author of a textbook of human osteology. Dr. H. R. R. Grieve is a member of the New South Wales medical board and of the Federal Council of the B.M.A. in Australia. A few years ago he was president of the New South Wales Branch, which he had also served as honorary secretary for several years. Dr. Ralph Whishaw is honorary physician to the Royal Hobart Hospital in Tasmania. A cardiologist, he has been a vice-president of the Royal Australasian College of Physicians and is a former president of the Tasmanian Branch of the B.M.A.

We are here able to mention only a few of those members of the medical profession whose names appear in the New Year Honours, but a full list will be published in next week's *Journal*.

SECOND CHAIR OF RHEUMATOLOGY

Dr. E. G. L. Bywaters has been appointed the first occupant of the new chair of rheumatology at the Postgraduate Medical School of London. The chair is only the second of its kind in the country. It was instituted last month by the Senate of London University, and like its predecessor at Manchester University has been endowed by the Empire Rheumatism Council. Dr. Bywaters, who has often contributed to this *Journal*, is known particularly for his researches on juvenile rheumatism at the Canadian Red Cross Memorial Hospital, Taplow, and for his work on crush injuries during the war. He is also a member of the editorial committee of *Annals of the Rheumatic Diseases*, the journal on rheumatology published by the B.M.A. in close collaboration with the Empire Rheumatism Council.

We record with great regret the death on January 1 of Sir Ernest Kennaway, F.R.S., professor emeritus of experimental pathology in the University of London.

TORSION TESTIS AND ITS TREATMENT

REPORT OF A BILATERAL CASE

BY

A. WILFRID ADAMS, M.S., F.R.C.S.
Surgeon-in-Charge

AND

N. SLADE, F.R.C.S.
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Genito-Urinary Department, Bristol Royal Infirmary

Testicular torsion still receives scant attention although exhortations abound in surgical literature, of which that by O'Conor (1933) is a good example, emphasizing the serious outcome of neglect of the lesion. Rarity of it may be pleaded, but this is a doubtfully valid excuse, resting more on failure to recognize the condition than on fact. Present chances for a twisted testis are poor, surgery saving only 50% and in the rest partial atrophy is likely. Sometimes the opposite organ also suffers, and the victim may become a eunuch.

The papers by Burkitt (1956) and Chambers (1956) provide a further reason for reviewing the subject. They stress that if the testis is to have a better fate the onus of treatment must be mainly on the G.P., not the specialist.

Aetiology

The chief predisposing cause is varying degrees of failure by the gubernaculum to draw down the testis into the scrotum from its developmental birthplace by the kidney. In about half the cases torsion occurs in the inguinal testis. Another developmental imperfection explains cases occurring in the fully descended organ—namely, too spacious a tunica vaginalis, which allows the testicle to fall forwards and the cord to twist. This is due to the failure of the peritoneal processus vaginalis to close behind the testicle as it descends. A cul-de-sac remains, investing the spermatic cord above the testis and in continuity with the tunica vaginalis. In the bilateral case reported below (Fig. 1) the patency extended 6 cm. up the cords on both sides; while in another patient a still more infantile state was found, reaching nearly to the level of the internal abdominal ring with a corresponding mobility of the testis (Fig. 2). Fig. 3 shows the normally closed tunica level with the caput epididymis.

Campbell (1948) postulates a different aetiology in the neonatal cases in which the torsion is outside the tunica vaginalis—that is, a torsion of the cord—and explains how the testis in the newborn may be withdrawn from the scrotum without division of any tissue—a fact first noted by Astley Cooper two centuries ago, and more recently by Cooper (1929).

The common age incidence is from puberty to 30 years. Ewert and Hoffman (1944) state that torsion varies from a partial twist to three or four complete twists. Fig. 4 depicts the main clinical types, including the rarest—the intra-abdominal torsion, usually found with a cancerous testis.

Exciting causes by way of physical strains are variably present, and often the onset is during sleep or even while sitting in a chair and making a movement of crossing the knees. Unconscious thigh movements during sleep or an overactive cremasteric reflex may provoke some cases (see below).

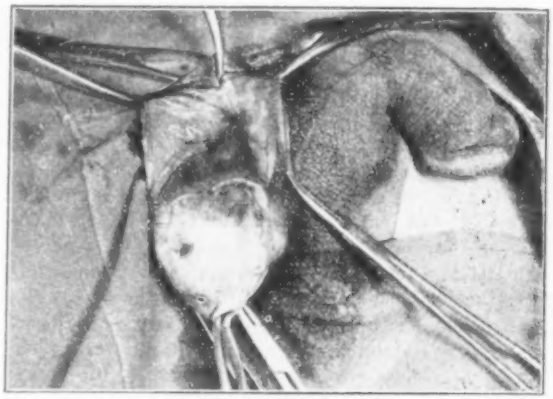

FIG. 2.—Patency of processus vaginalis from tunica to near internal abdominal ring.

Pathology

When torsion occurs in the retained testis the organ is usually cancerous and torsion is accompanied by bursting of the testicular mass with fatal results (Charendoff *et al.*, 1951).

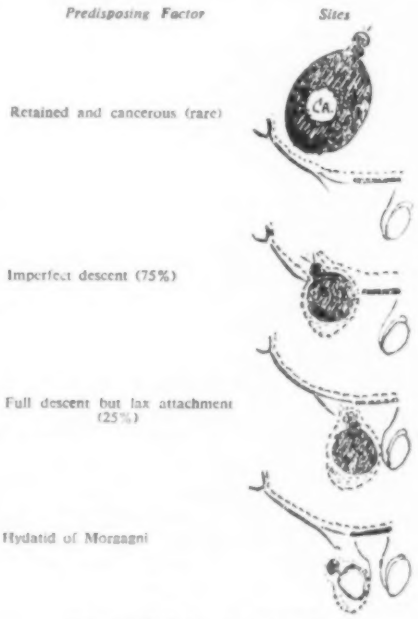

FIG. 4.—Varieties of torsion sites.

FIG. 1.—Acute torsion of right spermatic cord: orchidectomy for gangrene.

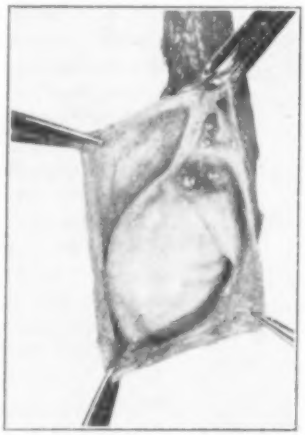

FIG. 3.—Tunica vaginalis closed over caput epididymis — normal anatomy.

In torsion of both the partially descended, with its processus vaginalis usually open, and the scrotal testis the tense swollen organ is surrounded in the course of a day or two by oedema, ecchymosis, and cellulitis spreading to the scrotal wall. Blood may be mixed with the secondary hydrocele. The spermatic artery being an end-artery, total ischaemia often results. The vestigial legacy is a soft miniature testis; in a case of ours it was 1.5 cm. in diameter. Biopsy of this removed relic showed: "The testis is entirely necrotic and largely calcified. There is no cellular reaction and changes are ischaemic. There is no evidence of syphilis or malignancy—ischaemic necrosis." It was removed during prostatectomy on a man of 70 instead of the routine vasotomy. The patient could not recall past trouble in the testicle. His opposite testis was normal and routine vasotomy was done. Some cases of early gangrene go on to suppuration.

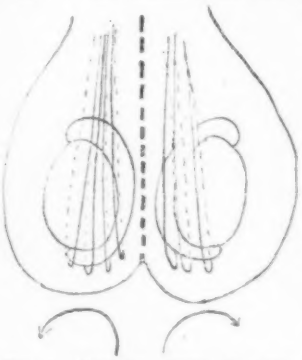

FIG. 5.—Testicles shown in "cremasteric sling": opposite direction of usual twists, right and left sides, indicated by arrows.

Although spontaneous or therapeutic detorsion saves the testis, variable degrees of fibrosis follow. In the chronically recurring lesions a substantial testis may remain despite multiple attacks, as in the case reported below. Torsion occasionally involves merely one of the genital developmental relics at the upper pole of the testis —for example, the hydatid of Morgagni, which swells to 1–2 cm. in diameter, and with intense reactionary cellulitis around may resemble torsion of the body.

In the left testicle the twist is usually clockwise, and in the right anti-clockwise. The rotation, encouraged by a lively cremaster, is unlikely to be towards the rigid mesial septum, but outwards. We suggest this may explain the usual direction of the torsion (Fig. 5).

Symptomatology

Torsion presents itself in three distinct clinical categories: (1) transient recurrent aches or minor colic; and (2) acute, variably ischaemic, attacks: (*a*) early phase, testis and epididymis definable; and (*b*) late phase, testicle obscured by surrounding inflammatory exudate. In some histories there may be a mixture of these events from time to time. The following case, during its lengthy history, illustrates all three types.

(1) At the age of 18 the patient had spells of continuous aching and a twisted sensation in the right groin which began to trouble him, awaking him during the night and lasting for about 20 minutes. The testicle hardened, but by the next morning the whole trouble passed off and he worked as usual. He did not have the doctor then or for the many minor attacks thereafter. Such a history is a very helpful diagnostic pointer for the doctor if he elicits it when a severe attack compels the patient to see him.

(2) At 19 years the patient had the first major attack and saw his doctor, who gave no diagnosis but bandaged the scrotum. At 22 years the next very bad attack occurred, with vomiting. The doctor arrived quickly, diagnosed torsion testis, and immediately sent the patient to hospital, where the specialist amended the diagnosis to acute epididymitis and treated with antibiotics.

(3) In his third severe attack (May, 1956) he was seen by us for the first time late on the fourth day. It had developed during the night: pain disabled him and recumbency relieved it, though exacerbations occurred. The right half of the scrotum was thrice as large as normal. Cellulitis and oedema of the skin anteriorly were present. Acute tenderness to the touch or on passive movement in any direction (Prehn's sign) hindered attempts to define the testicular elements: but, whereas the fingers sensed elasticity in front, there was irregular hardening over the region of the cord at the back. Apart from a tired look, he appeared in no obvious discomfort, lying with the homolateral hip mildly flexed and abducted. Slight fever was present, but no constitutional upset.

He had no past history of urinary disease. There was nothing amiss per rectum and the laboratory reported normal urine. Acute epididymo-orchitis was erroneously diagnosed, after failing to note the significant absence of collateral genito-urinary disturbance and to extract the history of previous attacks, an almost infallible token of torsion.

Diagnostic Features Summarized.—Sudden pain, which quickly intensifies in the lower abdominal quadrant or scrotum, follows physical stress or may supervene during sleep. The testicle at once swells and hardens. The patient guards against movement of the testicle, which is extremely tender. Per rectum nothing abnormal is to be felt. Constitutional upset is lacking, although vomiting or a mild febricula may be recorded. Urinary and intestinal disease are absent. History of former similar attacks may often be elicited.

Differential Diagnosis.—In the case of the inguinal testicle, strangulated hernia, orchitis of mumps, and adenitis have to be excluded. In the scrotal case the common mistake is to diagnose acute epididymo-orchitis or acute forms of hydrocele, haematocele, or pyocele. Owing to diffusion of pain into the adjacent peritoneum, appendicitis or intestinal or reno-ureteric colic may be misdiagnosed. Mild recurrent torsion is apt to be dismissed by the doctor as testicular neuralgia or cremasteric spasm.

Treatment

Efficacy is proportional to immediacy. Because the seminiferous tubules are very intolerant to ischaemia, release of the strangled artery is as urgent for the testicle as tracheotomy is to save the life of the individual. Measures vary with the clinical types.

Acute Stage.—Once the doctor diagnoses torsion it is incumbent on him to attempt immediate detorsion of the cord and restore the spermatic pulse at once. An hour later may be too late. The manipulation may be unbearable without local analgesia. Usually a clockwise direction is needed to undo the right testis and an anticlockwise direction for the left. Relief is maintained by a suspensory bandage. If this fails, open operation must be arranged expeditiously. In the first day or two adhesions are still soft and untwisting is feasible. Hot cloths may stimulate a sluggish circulation. Unless obviously dead, the testicle is better fixed and retained in the hope of its survival. Late sloughing and sepsis may necessitate drainage. Furthermore, operation may find its justification by revealing a strangulated hernia.

Acute Torsion Seen in Later Stage

At open operation, in the later phase of an attack, adhesions may have become organized, preventing untwisting: gangrene calls for ablation. Where, however, strangulation of the artery has been incomplete, detorsion may already have occurred or be feasible and sufficient viable tissue may be present to merit preservation of the testicle.

Concurrent herniotomy is done in the cases of patent processus vaginalis.

In a neonatal case conservation is preferred to opening the scrotum. Glaser and Wallis (1954), reviewing the literature, point to the futility of surgery, since in no case yet reported has the testicle been saved. Longino and Martin (1955) advise that, where detorsion fails, the testicle should be retained for its possible endocrine value.

Orchidopexy, apparently not considered by Birkitt (1956) or Chambers (1956), plays a useful part in torsion. It prevents recurrent torsion after reduction, spontaneous or manipulative. In addition, contralateral orchidopexy is especially indicated where one testicle has suffered or been destroyed, as there is a significant incidence of bilateral torsion. Thus, within a few months of losing his right testicle, a repetition of mild attacks began in our patient's remaining testicle, and his anxiety was aggravated by plans

of marriage in 1958. In January, 1957, operation became urgent because of two rather severe attacks despite the precautionary use of a suspensory bandage by day. Orchidopexy, during a quiescent phase, revealed a testicle of normal appearance, but the typical stigmata of lax attachments were present, nodding forwards towards the horizontal owing to a narrowed mesorchium, and the vaginal tunic prolonged 6 cm. up the cord.

For orchidopexy we favour a simple Jaboulay procedure combined with an anchoring nylon suture through the skin and lightly catching the tunica albuginea.

Summary

Torsion of the spermatic cord affects a most accessible organ, yet the profession still fails miserably both in diagnosis and in treatment of it. Although uncommon, it is a serious malady incurring loss of the testicle in half the operated cases.

In severe twists, with total arrest of the spermatic circulation, ischaemic necrosis is inevitable unless the doctor performs manual detorsion within an hour.

Doctors called to cases of sudden inguino-scrotal pain in youths or young men should respond with the utmost haste. If they diagnose torsion, they should themselves undertake manipulative detorsion at once. Only thus can there be improvement in the percentage of testicles saved.

If surgeons confronted with an acute scrotal swelling of uncertain diagnosis give up guessing and promptly explore, they will often discover a torsion which, in cases of partial ischaemia, may still be effectively untwisted. At the least, operation establishes a firm diagnosis, whereas all too often clinical diagnosis fails and the cases are treated for acute orchitis.

Orchidopexy prevents recurrent torsion and is advisable in the opposite testicle also, because patients are prone to bilateral torsion.

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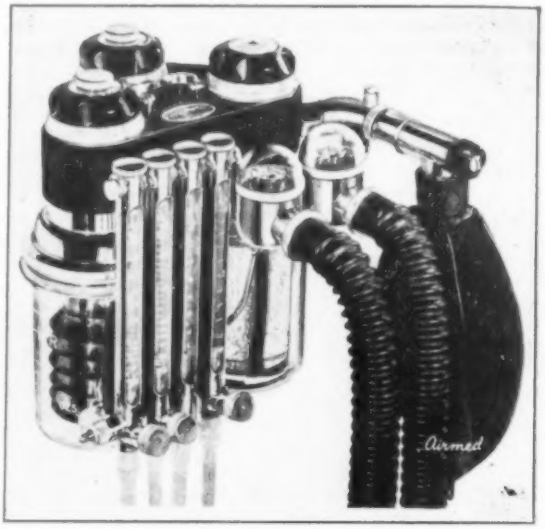
Preparations and Appliances

MODIFICATIONS TO THE MARRETT APPARATUS

Dr. H. REX MARRETT, consultant anaesthetist, Coventry and Warwickshire Hospital, writes: Since the introduction in 1948 of the Marrett anaesthetic apparatus there have been many advances in anaesthesia and consequent changes of techniques. It is because of the latter that alterations in design have been made for the purpose of safety and greater efficiency. Some methods, such as insufflation, have become practically extinct except for use with the Boyle–Davis gag in child tonsillectomies. Others are new, such as the rapid inflation of the lungs following the use of the relaxants during induction.

The bag-control valve on the first model was designed so that the bag could be shut off during the insufflation technique. Owing to the present-day method of using by-pass oxygen after the relaxant it has been thought safer to prevent the closure of the rebreathing bag, thereby allowing the tension of the thin rubber bag to give an indication of the pressure in the circuit and in the patient's lungs. The real danger is present when a junior anaesthetist inserts an endotracheal tube immediately after an ultra-short-acting relaxant without first inflating the lungs, and then turns on the oxygen by-pass for subsequent inflation with the bag control drum in the "shut" position. The bag mount has been moved to the right of the expiratory dome so that it can be more easily seen, and is attached by a tapered fitting,



so enabling a "walk around" bag assembly to be easily connected, with obvious advantages to those using controlled respiration.

Another safety feature is that instead of the by-pass oxygen being directed through the flowmeters it now passes direct to the patient's side of the inspiratory unidirectional valve. Thus the risk of decanting liquid ether or trichlorethylene into the machine, should the jars be overfilled and a control inadvertently be left "on," is entirely eliminated.

With the increasing use of colour-indicating soda lime, the absorber, which was of metal construction, now consists of two glass jars fitting one inside the other, the inner jar holding 1 lb. (450 g.) of soda lime. The inner jar is automatically guided into position by means of a simple spring when the outer jar is screwed into the body of the machine. Glass jars have many advantages: they allow quick observation of the change in colour of indicating soda lime and are easy to keep clean. An airtight fit is now more certain because the seal of the outer jar is at the top instead of the bottom, thus being free of soda lime granules. A jar similar to the outer soda lime one is now used for the ether vaporizer, thus permitting larger cones to be used, giving an even smoother ether induction.

The soda lime control can now be set either to "circle" or to "to-and-fro" absorption. With the previous model both inspirations and expirations passed through the soda lime—that is, "to and fro"—which was to provide maximum absorption efficiency, but with the attendant disadvantage of slight dead space between the top of the soda lime and the bottom of the control drum. This dead space was sufficient, when added to that in the facepiece, to cause an increase in rate and depth of respiration in small children. By selecting "circle," expirations only pass through the soda lime, thereby eliminating all dead space in the machine. The resistance to respiration under working conditions tested with a sensitive gauge has never been seen to rise above 1.5 cm. of water on the "to-and-fro" circuit and not above 1 cm. on the "circle."

The machine is manufactured by Airmed Ltd., Harlow, Essex, who provided the illustration.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Immunization Confusion

SIR,—The following plan for routine immunization of children in this country and at this time—i.e., at 2, 3, and 4 months, whooping-cough; 5 and 6 months, diphtheria (formol toxoid); 7 months, vaccination; 8 months and 9 months, tetanus toxoid—is based on the following considerations. (1) The necessity for early protection against whooping-cough. (2) Reducing the risk of injection poliomyelitis by using separate antigens and by using formol toxoid as the antigen against diphtheria. (3) The desirability of producing active immunity against tetanus. There are two good reasons for the latter: first, the obvious one of protection against a deadly disease; secondly, protection against the risk of severe A.T.S. reactions in the increasing proportion of children who are receiving A.T.S. There is much to be said for using booster doses of toxoid in the actively immunized child in the case of subsequent injuries where normally A.T.S. would be given, in order to avoid such reactions.

In this area we are trying to follow such a plan on the advice of our local medical officer of health. We immunize some children at home or in the surgery, but a majority are immunized in six clinics which we run in the town and in five of the surrounding villages. The amount of work involved is considerable. The trouble is that the number of attendances involved is disliked by parents and children. Also, since any injection may precipitate poliomyelitis, one wonders whether the risk of more injections with less risky antigens does not outweigh the risk of fewer injections with more risky combined antigens. But much the most important objection is that the children of the less conscientious mothers just will not be brought to the clinic for the full course of injections, and it is in some ways for the less conscientious mothers one has to cater; others will see that their children are fully protected whatever the plan. This will become even more true when the addition of two injections against poliomyelitis makes the list even more formidable. There are, therefore, strong arguments in favour of the use of combined antigens, unless one is genuinely convinced that they are either so much less effective or so much more dangerous that the tedious and lengthy plan outlined above is justified.

The most urgent need is, however, for a national policy on immunization. At the moment individual doctors and different areas are following totally different plans, and parents seldom know when they join one's list what diseases their children have been protected against. It is no exaggeration to say that a state of confusion exists on the whole policy of immunization. There is a need for those best qualified to advise to draw up a plan for the whole country. It need not interfere with any doctor's right to follow a system of his own devising if he wishes. This letter is written in the hope that it will stimulate someone to devise such a plan, lest in its absence one of our most effective weapons against childhood disease is made less effective by an unnecessary state of muddle.—We are, etc.,

I. S. L. LOUDON.
C. W. SEWARD.
J. K. HAWKEY.

Wantage, Berks.

Amnion Implantation in Peripheral Vascular Disease

SIR,—It was with great interest that I read Mr. H. Dendy Moore's article (*Journal*, December 7, p. 1350) on amnion implantation in peripheral vascular disease, and with even greater interest that sympathectomy had been used with the object of improving claudication. I have found that sympathectomy is rarely of benefit for the treatment of claudication *per se*, but can be done in stage III cases where there are skin changes in the limb. Patients in whom ischaemic changes of the foot have occurred will benefit if it has previously been shown that a chemical sympathectomy decreases the vasoconstrictor element in the foot. It is on purpose that I have mentioned sympathectomy first, because it may explain the results published by Mr. Dendy Moore. As sympathectomy would only be resorted to in stage III or fairly advanced atherosclerosis, it appears that his cases were in this category. My own cases reviewed to date are parallel—namely, good results following amnion implantation in stage II but not so in stage III. If stage III cases do improve it may take as long as one year before improvement becomes obvious. Most of my original series of cases[1] published in 1956 were treated with amnion prepared in our own hospital and a smaller percentage with commercial amnion, but it must be stated that the commercial product is not so effective. An explanation may be in the treatment it receives, such as autoclaving and perhaps too vigorous cleaning. Mr. Dendy Moore's seven cases were all suffering from fairly advanced arterial disease, they all had sympathectomy and amnion implantation, and they appear to belong to stage III.

Case 1 had rest pain and cold, clammy feet and a walking distance of 30 yards. Few cases, if any, in stage II have rest pains and as little walking distance as 30 yards. Cases 3, 4, 5, and 6 presented with skin changes of the feet, which in addition were cold; Cases 3 and 6 had blue toes indicating the severity, and late stage. These four cases would probably have benefited from a homograft. Cases 2 and 7 are of special interest because they were both women; that 2 cases out of 7 were women is a high percentage, as it is known that roughly 10% of all claudicants are women, and in my own series the percentage is considerably less. Out of some 120 cases 9 were women. Several women patients maintain that they have to stop after walking 50–100 yards. On examination the arterial circulation is within normal limits with a good oscillometric response. They are often women who have had venous thrombosis following childbirth, and these I have called pseudoclaudicants for want of a better word. These remarks certainly do not refer to Mr. Dendy Moore's cases, who, from their history and presentation, appear to be true claudicants, but it is possible that they may, in addition to their arterial disease, also have had some venous blockage, which makes treatment so extremely difficult. I do not think that seven cases are enough to provide evidence of therapeutic success or failure, especially as there were no substantial subjective findings.

In conclusion, I would like to state that Mr. Dendy Moore's article was most useful in that it agrees with my contention that amnion implantation is of much less value in stage III claudication, and I hope that in future he will give this treatment a trial for stage II cases.—I am, etc.,

London, W.C.2. E. TROENSEGAARD-HANSEN.

REFERENCE

1 Troensegaard-Hansen, E., *Brit. med. J.*, 1956, 2, 262.

Traffic Delays

SIR,—Further to Dr. C. W. Coole's letter (*Journal*, December 7, p. 1370) regarding traffic delays in large cities and the difficulties most of us experience in obtaining parking space, I learn with dismay that many of my colleagues in and about the Harley Street area have had their cars removed by the police.

I understand that the M.P. for St. Marylebone is to raise the question in Parliament, but it occurs to me that a solution could be found to the general problem if legislation were provided to enable medical practitioners to display a plate with the letters M.D. in, say, red, on their windscreens, fixed with suction pads so that the plate need not be a permanent fixture and a source of annoyance when the practitioner is on holiday, etc. Legislation would be required to impose fines for fraudulent use or abuse, and also to

ensure the helpful co-operation of the police in their difficult work. A system of M.D. plates has worked very well in the United States of America for many years now, and medical personnel often receive priority from both the police and public alike when the situation demands.—I am, etc.,

London, S.W.1. H. GOUGH-THOMAS.

Anxious Patient and Worried Doctor

SIR,—Your annotation on "The Anxious Patient and the Worried Doctor" (December 21, p. 1483) has failed to reassure at least one of the latter. It was on account of an increasing awareness of the difficulties involved in dealing with "neurotic" patients that I undertook an experiment in my practice with the help of a psychiatric social worker, and a description of this has been given elsewhere.[1] For the same reason I subsequently joined one of the G.P. research seminars held at the Tavistock Clinic.

I am uncertain as to the value of some of the opinions expressed in the annotation. The emotional reaction of many doctors to the neurotic is said to be "out of all proportion to the demands of the patient." It might be more true to say that the emotional reaction of the doctor is exactly what is demanded by the patient, and this reaction, if recognized, may be used as a guide to the patient's difficulties in interpersonal relationships. Some patients need "potent" doctors; they are always extolling our virtues and carry out our instructions with meticulous detail; others need "impotent" doctors, and for them nothing goes well, every tablet upsets them, every pronouncement is questioned. Yet normally we regard only the latter group as "neurotic," for they cast doubts on our ability as physicians, hitting us where it hurts, for most of us need to be "potent" doctors.

"If it is decided that the problem is one of anxiety, then unqualified reassurance must be given." Strong, forceful words. It might be profitable to see what happens in practice when this is carried out. Mrs. J. comes to her practitioner complaining that she has "far-away feelings" in her head. There being nothing in the history or physical examination to suggest an organic lesion, the doctor pronounces "there is nothing wrong with you, Mrs. J.," and possibly "potentiates" his reassurance with a nice new American drug. He writes "nerves" or "anxiety state" in his notes, and leaves it at that; it is rather like hearing an apical presystolic murmur in a dyspnoeic patient and writing down "C.V.S." or "Heart." It is merely a question of level of diagnosis. What happens to the patient? She may thank her doctor and go. Whither? To someone else? To suffer in silence? Indeed, she may even abandon her "far-away feelings," having "offered" them (as Dr. Michael Balint says) unsuccessfully to her doctor, only to come back, days, weeks, or months later, with a sore throat, for example, which she has had "for weeks, Doctor." N.A.D. again. Then what? Might it not be that the patient is trying to communicate something to us that she is unable to verbalize? So what good does our reassurance do her? If the doctor is honest he probably even fails to reassure himself. Occasionally, of course, such a manœuvre appears to, and in fact does, work. I often wonder why; I believe it is due to the natural resilience of the particular patient rather than to our own endeavours. Alternatively the patient may not accept the reassurance from the start. "You are not taking enough notice of me, Doctor," as it were, and this is where more trouble starts. To take the line of least resistance, multiple referrals, multiple investigations, and "organize" the illness, often irreversibly, along organic lines? Or perhaps to bully the patient, "take it or leave it!" No, Sir, the problem is not as simple as you expound it.

Quite rightly you state that "the importance of the listening ear cannot be overemphasized." But is listening enough, especially when it is done with a protectively closed ear? I used to listen until my head was bursting and I would have given anything to get the patient out of my consulting-room, and still I was no wiser. But as a result of my experiences with the psychiatric social worker, Mr. Eugene Heimler, and in the seminars at the Tavistock Clinic, slowly but surely the words of the patients are beginning to mean something, something that may be utilized in their treatment. It is a new language, an entirely new vista of "physical signs." And the reason I am not reassured? For every time I say to a patient, "Yes, there is certainly something wrong, but not where you think it is," I know the difficulties and time-consuming labour that lie ahead, and, with an N.H.S. list of patients of sufficient size to maintain a decent standard of living, there just isn't the time to do justice to more than a fraction of the people in this category; but I will not "reassure" the others.—I am, etc.,

London, N.11. NEVILLE DAVIS.

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[1] Davis N., *Lancet*, 1957, **1**, 160.

SIR,—In your annotation on this subject (*Journal*, December 21, 1957, p. 1483) you mentioned the problem of the neurotic patient, and discussed the way this was handled at the recent conference in London held by some Faculties of the College of General Practitioners and the Society for Psychosomatic Research. I feel it should have been made more clear that the subject of the conference was "Stress Problems in General Practice" and that it was agreed that patients with stress disorders such as dyspepsia, asthma, certain skin disorders, etc., needed to talk to their doctors about their stress just as much as the "neurotics." Furthermore, you mentioned the need for unqualified reassurance if the doctor finally decided that his patient's problem was due to anxiety. Any doctor who has thought seriously about this will realize that in such cases the only person who is reassured that there is no need for worry, because there is no evidence of organic disease, is the doctor himself. Reassurance is not therapy for the anxious patient. Therapy must include a ventilation of feeling by the patient and an achievement of insight, and the practitioner's problem is how to achieve this in a short period of time.—I am, etc.,

London, W.8. H. STEPHEN PASMORE.

"Nomen Proprium"

SIR,—Since I was the first to draw attention in these columns to the problem of the unnamed drug (*Journal*, June 4, 1955, p. 1392), may I be permitted to comment on the communication by Mr. C. Wilson Peck and Mr. G. Bryan (*Journal*, December 7, p. 1366)? I was greatly pleased to read of the "growing practice by prescribers of disclosing to patients the identity of prescribed medicines." The correspondence which followed my original letter showed that many practitioners had been troubled by unnamed tablets. The cases of poisoning by "mistaken capsules" prove that this is a matter of some urgency, and I believe I am right in saying that the members of the medical, and not those of the pharmaceutical, profession are best qualified to judge the pros and cons of the "anonymous" medicine.

The points put forward by the above correspondents in favour of the latter seem to me rather weak: (1) Scheduled drugs are only dispensed once and can therefore not become dangerous even when they are named. (2) I do not see any reason for assuming that self-medication or demands for a special medicine will increase when the name of the drug is disclosed. Those patients who intend using their medicine at a later date usually put some indication as to its use on the bottle, and everybody can in any case have his medicine renewed by presenting the original prescription or even the bottle alone to his chemist, provided the drug is not on the dangerous drugs list. I submit that self-medication with a named drug may still be safer than with an unnamed drug. Furthermore, it is easier for the physician to respond appropriately to the demand for a named drug than to the request for a white tablet "which had previously helped" but whose identity has first to be established. (3) Why should the pharmaceutical profession be so anxious to prevent "embarrassment of the physician" arising from the fact that the patient may read the leaflet which original packings often contain? Can these leaflets not be removed prior to dispensing? Besides, I firmly believe that the conscientious physician will be well acquainted with the

contents of such leaflets and that he will be able to give his reasons for deviating from any printed instructions. (4) Why do Mr. Wilson Peck and Mr. Bryan presume that the name on the bottle will be used by the physician as "an *aide-mémoire* in repeating prescriptions" and not as a method of identification, so urgently required when several drugs have been prescribed simultaneously? (5) As regards "the most serious risk" of a drug being used when it has become inert or even toxic, the only obvious safeguard against this risk will be to issue original bottles only and to compel the manufacturer to state the date of expiry on every container in the case of perishable drugs as it is done for antibiotics, etc.

If one also considers how much time, labour, and cost would be saved and how much delay be avoided if it were no longer necessary to refill, number, and record every drug for dispensing (except, of course, the dangerous drugs), it seems logical and highly desirable to bury "the tablets" and "the mixture" and to mark prescriptions with "Omit N.P." in those exceptional instances when it is undesirable to disclose the identity of the medicine.—I am, etc.,

London, W.1. H. UCKO.

Seat Belts for the Motorist

SIR,—Recently on a visit to the United States I was given a lift into town by a member of the staff of one of the hospitals I visited. Before starting he inquired whether I minded using a seat belt, as his car was fitted with these belts. He told me that a serious study of the mechanism of injury in road accidents is being undertaken in the United States, where the accident rate is high, and one particular point which is being investigated is whether these belts would help to reduce the chance of injury. He himself believed they would, and he always used a seat belt. I was most impressed by this suggestion, which is, of course, a standard practice in aircraft when taking off, landing, or flying in bad weather. I imagine the objective is a double one, mainly to prevent injury to passengers but also to prevent a sudden shifting of load.

On my return to this country I inquired of the first two patients in my ward injured in motor-car accidents of the mechanism of their injuries. In both the injury was due to their being thrown forward against the windscreen or front of the car, while other occupants who were not thrown forward were uninjured. It appears that seat belts would have prevented these injuries. I am writing to ask whether a study of the mechanism of injury in motor-car accidents has been made in this country, and whether there is evidence that the use of seat belts would reduce the incidence of injury. If no such study has been made, may I suggest the British Medical Association sponsor such an investigation? Should seat belts prove of benefit this would be a simple and inexpensive way of reducing the numerous injuries from motor accidents. It is possible that a seat belt would do for the motorist what the crash helmet has done for the motor-cyclist.—I am, etc.,

Brighton. L. W. LAUSTE.

Chlorpromazine Jaundice

SIR,—Dr. G. Hurst's letter (*Journal*, November 30, p. 1307) concerning the appearance of chlorpromazine jaundice after termination of treatment with the drug prompts us to report the following two cases, both occurring at the Bethlem Royal Hospital within the last five months.

A single girl of 39, with a strong family history of mental illness, was admitted suffering from her first acute schizophrenic illness. As she was hyperactive, therapy with chlorpromazine was begun, the maximum dose being 100 mg. thrice daily. After ten days, however, there was a sudden collapse with signs of peripheral circulatory failure, from which she recovered with energetic treatment. Chlorpromazine was immediately discontinued. Following this episode she developed an acute lobar pneumonia which responded to penicillin. Sixteen days after cessation of chlorpromazine therapy it was first noticed she was jaundiced. She was pyrexial, and on examination her liver was found to be enlarged and tender. Her serum bilirubin tests showed a positive direct reaction, the bilirubin level being 12.8 mg./100 ml. The other tests supported a diagnosis of obstructive jaundice. After three weeks her jaundice cleared up; she was treated with electric convulsion therapy and made a complete recovery.

A woman of 54, with no history of liver disease, was admitted with an agitated depression. She was given chlorpromazine, a maximum of 50 mg. thrice daily for seven days, when it was discontinued and electric convulsion therapy was administered. Fifteen days after stopping the chlorpromazine the patient developed jaundice. The patient was afebrile; the liver was neither tender nor palpable. Her stools were pale. Her serum bilirubin tests showed a positive direct reaction, the serum bilirubin level being 5.7 mg per 100 ml. The other tests again supported a diagnosis of mild obstructive jaundice. The jaundice cleared up in the course of seven days and the patient made an uneventful recovery.

Although jaundice is a common complication of chlorpromazine therapy, it is not often realized that it may occur after the drug has been discontinued. Failure to recognize this fact has resulted in several patients being subjected to unnecessary operative procedures.—We are, etc.,

S. BENAIM.
Beckenham, Kent. A. J. COPPEN.

REFERENCE

[1] Rawlings, K. O., personal communication, 1957.

Preparation of Skin for Electrocardiography

SIR,—I have read Dr. M. K. Browne's letter (*Journal*, November 23, p. 1238) with great interest. The exact measurement of skin resistance needs facilities which I do not possess, and my observations (*Journal*, October 19, p. 942) were based on standard tracings taken during the routine examination of patients. At first I compared the jelly and water methods in twenty cases, and I was surprised to find that the results agreed more closely than I had expected. I have also compared tracings with others taken on previous occasions when jelly was used, and they have agreed reasonably well.

There has never been any result which would suggest that an error of diagnosis would be at all likely, and I have certainly not yet seen a tracing which would indicate that disease was present when, in fact, the heart was healthy. I am not so sure about Dr. Browne's point about the position of the heart. Up to the present I have not encountered a misleading result, and I believe that the patterns obtained are quite reliable. Except in acute cases there is always *x*-ray control and usually a barium swallow as well, and I have not found any considerable discrepancy when comparing the results obtained by these methods of investigation.—I am, etc.,

London, N.W.1. JAMES MAXWELL.

Drug Firm Representatives

SIR,—I have just read with a considerable amount of sympathy Dr. D. J. Adderley's letter (*Journal*, November 23, p. 1243) on drug firm representatives. However, I must disabuse him of his delightful dream that Americans expect a private consultation fee for their visits, certainly in this area of the country. It not infrequently happens that during a busy afternoon three or four of them may be found in the waiting-room at one time, but usually they will accept the hint courteously if the suggestion is made that another afternoon might be quieter. A consultation fee would sugar the pill over here too. In that not too distant past when I "hung out my shingle" it seemed for a time that there were more pharmaceutical men in the world than patients.—I am, etc.,

New York. R. RUSSELL LANG.

SIR,—Dr. B. W. Paine (*Journal*, December 21, 1957, p. 1491) is right in assuming that drugs would be cheaper were expensive advertising not necessary to their promotion. The discouraging thing to anyone trying to make a good product available cheaply is the thought that it is virtually impossible because of the burden of advertising, packaging, and distributive costs that it has to carry. These items cost the

National Health Service much more than the drugs themselves. How to escape from this absurdity is a puzzle. An effective partial solution, however, would be to ban all direct advertising and for the profession to be approached only through an approved body capable of checking the claims made for a product. In short, the remedy for the present situation is largely in the hands of the doctors themselves.—I am, etc.,

London, W.C.2. G. T. HODGE, Managing Director, Mining and Chemical Products Ltd.

SIR,—Surely the question of "Live and let live" enters into this matter. Whatever and whoever these men represent, they have a living to make like ourselves, and a little courtesy is all that is needed. A doctor whom I once knew treated them with a studied rudeness, but, as he treated me in the same way, I came to look upon him merely as "one of those things" (to use the current jargon). The opportunity to relax into a brief coma whilst they are talking often gives me much relief in the inspissated gloom which often surrounds me during a prolonged session. One or two representatives adopt an austere professional air, and almost dare one to budge until they have finished what is virtually a clinical lecture. Such men, if not dangerous, are at least tedious. I find samples useful. They often remind me of the name of the product which I want to use but of which I cannot at the moment remember the name. Furthermore, I often hand out expensive and well-tried products instead of writing a prescription, and to that extent help to reduce the national drug bill. I can think of nothing more boring than sitting in a doctor's waiting-room "trying to look like patients" (*Journal*, December 21, p. 1491). I am glad I was never destined to do it.—I am, etc.,

Brighton, Sussex. G. L. DAVIES.

Poliomyelitis in West Africa

SIR,—Dr. G. L. Alexander's letter (*Journal*, November 23, p. 1241) is most timely. At the time of writing there is in Accra a minor poliomyelitis epidemic. During the past two months there have been 5 paralytic cases in Europeans—4 adults (age 18–43), 3 of whom died—and one fatality in a child aged 16 months; and 12 paralytic cases in Africans (2 adults and 10 children) with no deaths. Poliomyelitis vaccines of English and foreign manufacture have been on the open market here for the past couple of months and are readily bought over the counter at drug stores without prescription. Many commercial firms have immunized their expatriate employees and families. Dr. Alexander's suggestion that persons proceeding to the tropics be regarded as a priority class for poliomyelitis vaccination should be given serious consideration.—I am, etc.,

Accra, Ghana. F. C. HARRIS.

Obscure Abdominal Pain

SIR,—Your recent annotation on obscure abdominal pain (*Journal*, November 16, p. 1169) brings to mind another cause of abdominal pain which may cause diagnostic difficulty—the prolapsed intervertebral disk. Until I attended the clinic of Dr. J. H. Cyriax three years ago I hardly knew what a disk lesion was. Since then I have found that a general practitioner may expect to see in excess of a hundred disk lesions a year, and that some 5% of these cause abdominal symptoms which may be either acute or chronic. The following examples give an idea of what may be expected.

A girl of 14 presented with very severe pain in the right iliac fossa with great tenderness and guarding at McBurney's point. I made a diagnosis of appendicular colic, until further questioning revealed that the onset occurred suddenly as the patient got out of a chair. Straight leg raising was then found to be limited to 30°. Manipulation relieved her of her pain within five minutes. A boy of 10 presented complaining of pain in the umbilicus whenever he reached up. The history revealed that the onset had occurred suddenly three days previously as he bent down to tie up his shoe-lace. His pain was reproduced by flexion and extension of the spine. Manipulation relieved him of his pain within a few minutes. A man of 50 had an attack of cystitis. After treatment there was a relapse, so this time he was given a prolonged course of urinary antiseptics. Shortly afterwards he again presented complaining of pain in the suprapubic region and along the line of the left ureter. However, this time there was no dysuria, so root pain was suspected. On examination the pain was aggravated by extension of the spine. One session of manipulation reduced the prolapsed disk, which has not recurred. A man of 30 complained of pain in the left hypochondrium of a rather vague type. He was diagnosed and treated as dyspepsia. Some months later he visited me again complaining of lumbago and mentioned that his dyspepsia was not much different: in fact he could feel the pain as he stood in the surgery. When his lumbar disk was manipulated he complained of a sharp pain in the left hypochondrium. This session of manipulation successfully reduced both his thoracic and lumbar disk protrusions, neither of which has recurred. It is quite easy even for those on the look-out for disk protrusions to miss them.

Bowel symptoms also occur, but whether these are a direct or reflex result of the protrusion I have not yet discovered. A man of 30 with very severe lumbago had partial paralytic ileus for several days. Intervertebral disk protrusions can cause pain anywhere in the body except in the face; therefore no obscure pain, whether in the abdomen or anywhere else, is fully investigated until the question of a disk protrusion has been considered.—I am, etc.,

Brampton, Hunts. R. T. D. FITZGERALD.

Recurring Cystitis in Women

SIR,—I was glad to read the article by Mr. H. P. Winsbury-White (*Journal*, December 14, p. 1399). Before the war he gave me help with several urethral cases. My approach to the subject of an infected urethra came from my work on cases of pruritus, leukoplakia, and kraurosis. I found that recurring vulvitis was usually accompanied by tenderness on passing any instrument into the urethra and/or an exudation of a bead of pus from the urethra and adjacent ducts when one pressed on the anterior surface of the vagina. A caruncle in the urethra implied infection of the duct beneath it. Thus it happened that in 1942, at the request of the late Sir Comyns Berkeley, I wrote a paper[1] entitled "Pruritus, Leukoplakia, and Kraurosis." In that article I gave details of the method of zinc ionization of the urethra which cured the urethral infection. I agree with Mr. Winsbury-White that in many cases with recurring cystitis it is also important to deal with erosion and discharge from the cervix.—I am, etc.,

London, W.1. AGNES SAVILL.

REFERENCE

[1] Savill, A., *J. Obstet. Gynaec. Brit. Emp.*, 1942, **49**, 310.

Resuscitation

SIR,—There is at present on the market a machine named the "Stephenson Minuteman Resuscitator," supplied by British Oxygen, Ltd., which is designed for emergency and rescue work. It has been installed in numerous industries and also in some first-aid services. Many people think that, when available, it should replace the normal forms of resuscitation—i.e., Holger Nielsen artificial respiration. As far as I am aware, there has been no comment in the medical press regarding this type of machine, and I feel a strong word of caution is necessary. I cannot see how a machine of this type can be effective without the introduction of an intratracheal tube. The principle relies on alternating positive and negative pressure of oxygen supplied through a mask clamped firmly over the mouth and nose. It is suggested that a Phillips airway be inserted into the mouth. Surely, the air forced in under pressure will take the line of least resistance in a completely flaccid patient—i.e., it will travel down the oesophagus towards the stomach. I can see no reason why this air should decide to enter the trachea via the small laryngeal opening. Likewise, the negative pressure would draw on this reservoir of air or oxygen from the stomach.

The idea of such a machine for remote rescue is an excellent one, and I only hope that someone can prove to me

that it will work in practice. I cannot help feeling that old and tried methods should not be too readily superseded. Surely medical departments, before accepting a machine of this nature, should insist that it has the blessing of bodies such as the Medical Research Council or the Association of Anaesthetists? Other types of masks used in industry have to be Home Office approved—why not this one?—I am, etc.,

Derby. O. P. LLEWELLYN.

Treatment of Leg Ulcers

SIR,—We are glad that our report (*Journal*, October 12, p. 861) has stimulated discussion on the treatment of this common disabling condition. Although we have demonstrated the value of a technique not previously used in this country we feel that principles rather than details of treatment should be stressed. Most people agree that firm compression is the mainstay of treatment. Whether an adhesive, an elastic webbing, or a stockinette bandage is used is a matter of individual preference. (We prefer the stockinette method as a routine, since skin irritation is avoided, secretions are absorbed, and it is cheap.)

Instead of concentrating on different methods of compression (each of which has been shown to give good results), it would be better to concert our efforts in overcoming the appalling apathy with which many doctors and even patients view these leg ulcers. Eighty per cent. can be healed in a few weeks while the patient continues his ordinary work. We should no more be resigned to the presence of an open leg ulcer than we are to that of an open tuberculous cavity. With attention to detail and enthusiasm, ulcers can be healed in general practice. Every hospital should have a leg ulcer clinic where continuity of treatment is maintained. A clinic run by a frequently changing medical and nursing staff is useless. We all know that there is a small hard core of aged patients with large ulcers whose treatment is very difficult, but the majority can be healed in a few weeks. In our experience there is no more rewarding clinic.—We are, etc.,

KEITH BALL.
London, W.5. DAVID PHEAR.

Knock-knee in Children

SIR,—If it is of any value I am glad to give the figures for which Mr. D. F. Ellison Nash asks (*Journal*, December 14, p. 1437). Six of my colleagues never use splints; one "almost never"; one uses night splints for children with more than three inches (7.5 cm.) separation of the malleoli; and one uses them possibly more frequently. I should have liked to quote from some of the excellent letters I received, because several of my colleagues discussed the subject at length. But you are short of space, Sir, and, anyway, we are tending to wander away from the subject of Dr. Mary Morley's paper (*Journal*, October 26, p. 976) which provoked this correspondence.

I was encouraged in reading Mr. G. K. Rose's letter (*Journal*, December 14, p. 1437) in which he refers to the evidence from the Robert Jones and Agnes Hunt Orthopaedic Hospital that supports the conclusions reached by Dr. Morley. There is, however, just one point in his letter that I must answer. I agreed with what Mr. T. T. Stamm had said about the occasional need to satisfy parents that something is being done for a child with knock-knee (*Journal*, November 9, p. 1110), but I intended to convey the opinion that splints could be positively harmful.—I am, etc.,

London, W.1. H. J. SEDDON.

Substitute for the Souttar Tube

SIR,—Can we not give the apparatus used for intubation of oesophageal stricture its proper name (*Journal*, December 14, p. 1431), the Symonds tube? It was invented by Sir Charters Symonds, father of Sir Charles Symonds, and was in common use at Guy's when I was Sir Charters's dresser in 1911.—I am, etc.,

London, W.1. HENEAGE OGILVIE.

Obituary

Sir THOMAS DUNHILL, G.C.V.O., M.D.
Hon.F.R.C.S., F.R.A.C.S.

Sir Thomas Dunhill, extra surgeon to the Queen and consulting surgeon to St. Bartholomew's Hospital, died at his home at Hampstead on December 22, aged 81. His pioneer work in the field of thyroid surgery won him an international reputation. After a distinguished career in Australia before the first world war, he made a new and even more distinguished career in London and achieved the highest surgical honour in the gift of the sovereign as Serjeant Surgeon to King George VI.

Thomas Peel Dunhill, the son of John Webster Dunhill, was born at Tragowel, Victoria, Australia, on December 3, 1876. After leaving school he spent some years as an assistant in a chemist's shop to earn enough money to pay for his medical education. Winning an exhibition to Melbourne University, he took first-class honours in many of the examinations and was Beany surgical scholar. He graduated M.B. in 1903 and proceeded to the M.D. in 1906. After qualification he was house-surgeon to the late Sir Henry Maudsley at the Royal Melbourne Hospital and only two years later was elected to the staff of St. Vincent's Hospital, Melbourne. At the same time he set up in private surgical practice in Collins Street.

[Photograph by Paul Laib from the portrait by James Gunn, A.R.A., R.P.

Even as a house-surgeon Dunhill was taking a keen interest in the surgery of the thyroid gland, and practised the operation of thyroidectomy on goats—which he used to milk himself and then distribute the milk among his patients in the wards. His first paper on the treatment of exophthalmic goitre by partial thyroidectomy under local anaesthesia was published in the *Intercolonial Medical Journal of Australasia* in 1908 (vol. 13, p. 293). In those days the resection of one lobe of the thyroid together with ligation of a main artery on the opposite side was as much as most surgeons attempted. In 1908 Dunhill decided, after much anxious thought and discussion, to try to improve his results in the more severe cases of Graves's disease by resecting part of the second lobe. The outcome was highly successful, and Dunhill's methods were taken up and developed by surgeons all over the world. He himself possessed just those qualities needed for the intricate manœuvres of thyroid surgery, for he was a gentle, quick, and skilful operator. In 1909 he published in this *Journal* an account of 113 partial thyroidectomies performed under local anaesthesia. Three years later he visited the United States and Britain, and while in London he described his treatment of simple goitre to the Section of Surgery at the Royal Society of Medicine. In 1919 he published an outstanding paper in the *British Journal of Surgery* on the surgical treatment of exophthalmic goitre.

During the first world war Dunhill's brilliant work as a military surgeon attracted the attention of some of the leading surgeons in Britain. He immediately volunteered for

service with the Australian Imperial Forces on the outbreak of the war, and, serving mostly in France, he rose to the rank of colonel. In 1918 he became consulting surgeon to the British Army in France. Three times mentioned in dispatches, he was appointed C.M.G. in 1919. After the war he returned to Australia, but only for a short time, for in 1920 the late Professor George Gask, who was then forming the first professorial surgical unit in the University of London at St. Bartholomew's Hospital, invited Dunhill from Australia to be his first assistant. Gask had been one of those who had greatly admired Dunhill's work during the war, and, being eager to promote development in the surgery of the chest, he thought Dunhill was the best man for the job. It was a wise choice, for Dunhill brought great credit not only to St. Bartholomew's Hospital but to British surgery as a whole. He became, after Sir James Berry, the pioneer of thyroid surgery in Great Britain, and the younger surgeons who made such great advances in this field between the wars looked to him for guidance. He summed up his work in the Lettsomian lectures delivered before the Medical Society of London in 1937. Four years later the society awarded him its Fothergillian gold medal. Soon after he joined the staff of St. Bartholomew's Hospital, where in due course he became full surgeon and then, on his retirement in 1935, consulting surgeon, he published a description of his operation for the removal of intrathoracic tumours by the trans-sternal route, which marked a step forward in thoracic surgery. At the Royal College of Surgeons he gave the Arris and Gale lectures on carcinoma of the thyroid in 1931 and on diaphragmatic hernia in 1934; and in 1939 he received the distinction, unique for a surgeon practising in London, of election to honorary Fellowship, a rank usually reserved for the most distinguished of foreign surgeons. The College awarded him the Cecil Joll prize in 1950, and in the following year he delivered the Joll memorial lecture on the subject of thyrotoxicosis. He was elected a Fellow of the Royal Australasian College of Surgeons in 1930. Apart from his work at St. Bartholomew's, Dunhill had a large private practice and was consulting surgeon to the Queen Alexandra Military Hospital, Millbank, and to the London County Council.

Sir Thomas Dunhill was a member of the B.M.A. for 50 years and served on the Central Council from 1921 to 1936. He was also a member of the Dominions and other committees of the Association. When the Annual Meeting was held at Melbourne in 1935 he was president of the Section of Surgery. During this visit to Australia he had conferred on him the honorary degree of M.D. by the University of Adelaide. Many of the papers he wrote on general surgical subjects as well as on thyroid surgery were published in this *Journal*.

Quiet and courteous in manner and scrupulously careful and efficient in professional affairs, Dunhill deservedly won a very high reputation as a surgeon and had many distinguished patients. He was appointed Surgeon to the Royal Household in 1928 and Honorary Surgeon to King George V two years later. After George V's death in 1936 he became Honorary Surgeon to Edward VIII and, in 1937, to George VI. Appointed Serjeant Surgeon to the King in 1939, he became Extra Surgeon to the present Queen in 1952. Created K.C.V.O. in 1933, he was promoted G.C.V.O. in 1949, after King George VI had undergone the operation of lumbar sympathectomy. He was also one of the medical men attending the King in 1951 when a lung resection was performed. During the second world war Sir Thomas Dunhill was consulting surgeon to the Australian Imperial Forces, serving with the rank of brigadier.

Sir Thomas Dunhill married in 1914 Mrs. Edith Florence McKellar. There were no children of the marriage. Lady Dunhill died in 1942, survived by the son and daughter of her first marriage.

We are indebted to Sir JAMES PATERSON ROSS, P.R.C.S., for the following appreciation: The attributes of eye, heart, and hand which are regarded as essential for a surgeon belonged to Sir Thomas Dunhill in full measure. He was an excellent clinician and a master craftsman, undaunted by difficulty or danger when a bold approach was called for, yet whose courage was always tempered with wisdom which warned him to avoid the hazard predoomed to failure. In addition he was richly endowed with the intellectual gifts without which a surgeon cannot succeed.

That he had a first-class brain became apparent very early in his career, for he quickly surmounted the difficulties which a country boy necessarily encountered when gaining entrance to Melbourne University, and in the course of his studies for the M.B. he won every prize available to him. This would have ensured him a place on the staff of the Royal Melbourne Hospital, at that time the only teaching hospital there, had he been prepared to wait the 10 years or so for a vacancy. Because of his brilliant record, however, within two years of qualifying he was offered a post on the surgical staff of St. Vincent's Hospital, and having taken it he set about at once to have this hospital also accepted by the university as a clinical school. It took him two years to influence the right people and to achieve his objective, and thus St. Vincent's became the second of the present teaching hospitals in Melbourne.

His pioneer work on toxic goitre, started single-handed under conditions of extreme difficulty, had established his reputation in Melbourne by 1914 when he went to the war as a colonel at the age of 30. By 1918 he was consultant surgeon to the British Expeditionary Force in France, a position which he won partly on account of his surgical skill, but chiefly because of his wise judgment and the stimulating influence he exerted upon the younger surgical specialists. His return to a brilliant future in Melbourne after the war seemed a foregone conclusion, yet he was persuaded to abandon his appointments and practice in Australia at considerable personal sacrifice, and to become assistant director of the surgical professorial unit at St. Bartholomew's Hospital, a move which had the most profound effect upon surgery in London in general, and surgery at Bart's in particular.

It is only natural that the profession should regard his work on the thyroid gland as Dunhill's particular contribution to the surgery of his time, and nobody could question his pre-eminence in this field. But to concentrate too much attention upon the surgery of goitre is unfair to the remarkable advances he made in other departments of surgery, especially in the treatment of diaphragmatic hernia and of pharyngeal diverticulum. The study of his writings on these subjects should form part of the education of every young surgeon who needs to learn to-day, perhaps more than ever before, how progress in surgery could be made by following fundamental principles without the aid of the modern ancillary methods of anaesthesia, antibiotics, and biochemistry.

Those of us who were privileged to work with him learned much from his technique, but even more from his general approach to surgery. We learned from him that it is worth while to go half-way round the world to watch another surgeon at work, and to bring back the requisite tools for the job. And, almost complementary to that, we learned the importance of welcoming visitors from home and abroad, every one of whom has something of greater or less importance to contribute to the craft of surgery or to the management of patients. Everything surgical was of interest to him, and to-day we mourn the loss of a truly general surgeon and a most courteous and kindly man who had the gift of generating deep affection in all who knew him well.

A colleague writes: When Tom Dunhill came to St. Bartholomew's Hospital after the first world war as assistant surgeon to Professor George Gask he was, as he admitted in later years, diffident and nervous, but this cannot have lasted for long. It was a master-stroke on Gask's part to realize that this youngish surgeon, almost unknown in London surgical circles, born and bred in faraway Melbourne, could supply just what a somewhat conservative and self-satisfied London hospital needed—an injection of new blood from the Dominions. Gask had

known Dunhill well as consulting surgeon in France and was confident that he was right.

Before 1914 Dunhill had already operated on a very large number of patients with toxic goitres, and when he came to London in 1920 no one else possessed anything approaching his experience, or the confidence arising from it, in the performance of what was then a difficult and hazardous operation. His reputation in this particular field of surgery quickly grew until, within a few years, visiting surgeons crowded in embarrassingly large numbers to his theatre at Bart's, and his position as one of the masters of thyroid surgery in Great Britain was soon established. His appointment as surgeon to the London County Council in 1932 initiated the development of the thyroid clinic at New End Hospital and its growth into the unique endocrine unit that it is to-day. His colleagues at Bart's soon realized the quality of the newcomer, for Dunhill was no mere specialist. He was a "general surgeon" in the truest sense and applied his keen mind and outstanding surgical ability to all the current problems of the time, whether in abdominal, orthopaedic, or thoracic surgery. His opinion was constantly sought by colleagues in difficulties, and by 1930 his name was more widely known in the world at large than that of any other member of the staff of his hospital.

Although Gask and Dunhill worked together in perfect harmony, their natures were in many ways complementary. Gask was calm, calculating, academic, and deeply interested in the problems of medical education. Dunhill was excitable, intensely practical, and did not really like teaching; his life was the practice of surgery, and at Bart's he was not loaded with the usual burden of committee meetings and tutorial classes. As part-time assistant to the professor of surgery, he was free to develop a very large private practice, while still giving of his best in time and ability to his work in the hospital. No man has worked harder than he at his profession, and his surgical output was prodigious, such as could have been accomplished only by someone of unusual mental and physical toughness. But nothing came easily to Dunhill. His rapid rise to surgical pre-eminence in professional circles and in the Royal Household was only achieved at the cost of intense mental application, worry, and insomnia. He was a perfectionist in everything he undertook and no trouble was too great in achieving his aims. Every detail of surgical technique was closely thought out and practised until it seemed to be exactly right; the problems of each patient were given the utmost attention, so that the confidence of the individual was always at his command from whatever social class the patient came.

Dunhill did not care for teaching, because he knew he did not possess the gift of lucid exposition. He wrote with difficulty, and every paper that he published was hammered out with infinite toil and trouble, but he never shrank from publishing anything that he felt he ought to contribute to the sum of knowledge, whatever it might cost him. His surgical assistants did not find him an easy taskmaster, and a tense atmosphere was always present in his operating theatre. The anecdote of two distinguished American visitors being asked to leave the theatre because they talked during an operation is not apocryphal. Yet, whatever temperamental difficulties there might be in the "Dunhill atmosphere," his personality commanded the greatest loyalty and devotion from his subordinates. His intellectual integrity was complete, and everyone with whom he worked immediately recognized that here was an exceptional mind applying itself with honesty and tenacity to whatever problem was presented to it, and informing the movements of two strong and clever hands in the service of surgery.

Dunhill applied his mind with the same zeal to his pastimes, whether it was fishing, gardening, or the furnishing of his house with choice pieces of antique craftsmanship. Several years of ill-health and insomnia followed retirement from his profession, so that he could not fully enjoy the rest that he earned, but he followed with affectionate interest the fortunes of his many friends and paid several visits to Australia. Melbourne will share with St. Bartholomew's in mourning the loss of one of her most distinguished sons.

A. J. EWINS, D.Sc., F.R.S.

Dr. A. J. Ewins, formerly director of research at the laboratories of May and Baker Ltd. and the discoverer of sulphapyridine (M. & B. 693), died on December 24, 1957, aged 75.

Arthur James Ewins, who was born on February 3, 1882, was educated at Alleyn's School, Dulwich, and joined the Wellcome Physiological Research Laboratories as an assistant in 1889. Studying in his spare time, he graduated in science at London University in 1906 and became a full member of the staff of the Research Laboratories, where he worked with Sir Henry Dale. For the first three years of the first world war he was a member of the scientific staff of the Central Research Institute of the Medical Research Committee (the forerunner of the Medical Research Council), and then in 1917 he joined the staff of May and Baker Ltd., as a research chemist. Eventually he became director of research, retiring in 1952. Numerous publications in the *Journal of the Chemical Society*, the *Biochemical Journal*, and the *Journal of Physiology* bear witness to the value of the experimental work he undertook with his team of research workers.

In their search for more active sulphonamide drugs than sulphanilamide Ewins and his colleague, M. Phillips, synthesized a large series of compounds on which bacteriological studies were carried out by the late Sir Lionel Whitby at the Middlesex Hospital. One of these compounds, sulphapyridine, was found to have great therapeutic activity against pneumococci of several types and also against meningococci. Within a few weeks of the appearance, in 1938, of Sir Lionel Whitby's account of laboratory studies, G. M. Evans and W. F. Gaisford reported a successful controlled trial of M. & B. 693 in 200 cases of lobar pneumonia. From then on the drug became very widely used in pneumonic and other infections, and though it was eventually superseded by improved sulphonamides M. & B. 693 became a household word, typifying the great advances in chemotherapy that were being made at that time. Dr. Ewins was elected F.R.S. in 1943.

We are indebted to Professor G. A. H. BUTTLE for the following appreciation: Dr. A. J. Ewins commenced his scientific work in the early years of the century in association with Sir Henry Dale at the Wellcome Laboratories at Herne Hill. He worked on acetyl and other esters of choline, and in 1914 he accompanied Sir Henry Dale to the then newly established National Institute for Medical Research at Hampstead. Here he continued his work on acetylcholine and he also became interested in the production of new organic arsenicals. After joining May and Baker he was responsible for several new chemotherapeutic drugs, but the work for which he will be most widely remembered is the synthesis of M. & B. 693 or sulphapyridine. Tréfouël and his colleagues at the Pasteur Institute had shown that sulphanilamide was the active part of the molecule of the red "prontosil" described by Domagk in 1935. Although sulphanilamide was active against streptococcal, meningococcal, and gonococcal infections, it did no more than cause a slight delay in the death of mice infected with pneumococci, and many workers had tried to make modifications of the substance to increase the range of activity. A compound where a benzene ring was substituted for one of the hydrogens in the amide group had been found to be as active as sulphanilamide itself, and Ewins thought of trying the heterocyclic pyridine ring as a substituent in this position. He collaborated with the late Sir Lionel Whitby at the Middlesex Hospital, where the compounds were tested in mice infected with various organisms, including pneumococci. Sulphapyridine was found to be effective in mice against an infection of 10,000 lethal doses of a type I pneumococcus, and soon it was tested in a patient suffering from lobar pneumonia, with a successful result.

It is significant of Ewins's quiet and retiring nature that he never published a paper on sulphapyridine, and, although Sir Lionel Whitby acknowledged his work in his *Lancet* paper of May 28, 1938, Ewins himself never reported the

chemical work which led up to the synthesis. He continued making other useful chemotherapeutic drugs, of which stilbamidine and pentamidine for the prophylaxis and early treatment of trypanosomiasis and of kala-azar were published after the discovery of M. & B. 693 itself. The treatment of pneumonia by sulphapyridine has long been superseded, first by less toxic sulphanilamides and later by the still more effective antibiotics. It is to Ewins, however, that we owe the important step of making the first chemotherapeutic substance effective in this prevalent disease, the successful treatment of which has probably done more to increase the span of life than any other single therapeutic measure.

J. J. KEEVIL, D.S.O., M.D., D.T.M.&H.

Surgeon Commander J. J. Keevil, who had deservedly won a high reputation as a medical historian after his retirement from the Navy, died on December 16, aged 56.

John Joyce Keevil was born on July 21, 1901. From Marlborough he went on to Caius College, Cambridge, and continued his medical education at St. Thomas's Hospital, qualifying in 1925. In the following year he took the D.T.M.&H. and worked for a short time in the Malayan Medical Service before entering the Royal Navy in 1927. For two years he served as assistant to the professor of pathology at the Royal Naval Medical School. In 1931 he graduated M.B., B.Chir. at Cambridge and proceeded to the M.D. in 1936. During most of his years in the Navy he served at sea, and in the second world war he was in aircraft carriers in the Mediterranean and in the Atlantic, Arctic, Indian, and Pacific Oceans. In 1941, while he was in H.M.S. *Illustrious*, he was awarded the D.S.O. for great courage and devotion to duty in the face of enemy attack.

Keevil was always interested in history, and he began contributing articles on naval medical history to the *Journal of the Royal Naval Medical Service* from 1932 onwards. Keevil retired from the Royal Navy in 1946 and thereafter was occupied mainly in medico-literary work. In 1950 he was appointed keeper of the library of the Royal College of Physicians, and it was from manuscripts in that library that he collected material for his two books on seventeenth-century physicians—*Hamey the Stranger* and *The Stranger's Son*. Keevil's main work, however, was his *Medicine and the Navy*. The first volume of this was published recently, and the second volume is in the press.

Sir HENRY DALE, O.M., writes: When the very sad news came of the early death of John Keevil, even beyond the circle of those who knew him personally there must have been many who would be aware of the serious loss which medical scholarship has sustained. It is certainly not to be expected that qualifications such as his, for the special task which he had planned and undertaken only a few years ago, will soon, if ever, be found again in so perfect a combination. There have been many men of sound scholarship and medical experience, in many countries, ready to devote their special abilities to studies of the history of medicine in general, or of its development in special periods or in special directions. It may well seem strange, however, in this country especially, with its tremendous naval history, that there should have been no earlier plan than that which Keevil had made for a full-scale history of medicine in its relation to the Navy. Here, at last, was a man of direct experience and distinguished achievement in the medical service of the Navy, both in peace and in the greatest of wars, who was also an accomplished scholar, with a keen historical instinct and a fine literary sensibility, and who was eager to devote as many as might be needed of the years of his retirement to writing a history, as complete as he could make it, of medicine in the Navy, which he himself had loved and served. When the opportunity was provided, he had gone happily to work, and the first volume of his history had already been published, and had been received with warm, even with enthusiastic, approval in the circles best able to judge its quality. It is tragically sad that, though the second volume, bringing the history down to the second decade of the eighteenth century, is already in the press, and will in due course become available, the plan will then be left but half accomplished, and that, so far as can be seen, there is now no likelihood that it can ever be completed. Those of us who have had the additional great privilege of friendly contact with John Keevil himself are very sad at the loss of one in whom the charm of a conspicuously modest and sensitive personality was as attractive as his almost fierce devotion to truth and precision of detail. Their own keen sense of loss will quicken their sympathy for the deeper bereavement of his widow, herself an accomplished writer.

Sir ARTHUR MACNALTY writes: John Keevil has left the stage of life on which he played a distinguished and scholarly part. Beneath a reserved and at times critical manner he hid a warm and generous heart. In regard to himself he was modest and unassuming. It was only from others that I heard of his gallantry and courage when the *Illustrious* was bombed in the second world war. He was the first editor for the Naval contribution to the *History of the Second World War, Medical Series*. I found in him a friend as well as a colleague, and he rendered great service in collecting material for the Naval volumes of the *History*. But Keevil soon tired of office work and went to sea again, retiring in 1946. As a medical historian he had great gifts—an excellent style, a passion for accuracy, controlled enthusiasm, and industry. When keeper of the library of the Royal College of Physicians his rearrangement of the library after the vicissitudes of war was admirable, and he found time for scholarly research in his books on the two Hameys, distinguished members of the College in the seventeenth century.

The work by which Keevil will live is *Medicine and the Navy*. The first volume (1200–1649) was published last September. After reading my review of it, Keevil wrote to me as follows: "The second volume is almost finished and should be published next spring," and he added with characteristic fortitude, "I had a coronary thrombosis recently and have a good deal of trouble from cervical arthritis, but these hardly interfere with reading and writing." So to the end, giving of his best, that strong heroic soul has gone from us.

Lord AMULREE writes: To one whose friendship with John Keevil began when we were both freshmen at Caius in 1919 his premature death, at the age of 56, means the breaking of a precious chain. Even in those days, and certainly in the years after leaving Cambridge when we lived in the same flat in Harley Street, Keevil's interest in local and family history was an indication of where, ultimately, his medical interests were to lie. His Brazilian mother may perhaps have been the reason why he was not willing to settle down to practise in England, and may have led to his joining first the Colonial Medical Service and later the Royal Navy. In both of these positions his warm understanding of the troubles and difficulties of his fellows made him a rare and valuable member of the mess, for in Keevil the larger implications of a doctor's place were of great importance. Though physically frail, he was possessed of a high degree of mental and physical courage.

As a medical historian Keevil's reputation is assured. Of his important work on the history of medicine in the Navy one volume has already appeared: and it is typical of his modesty that he was amazed at the warm reception it received. But medical history was not his only interest: he worked hard, among other things, as a member of the Howard League for Penal Reform, and his death will leave a sad gap in many circles where justice and social inequality are considered. His private life was happy, and there are many who will miss him in his charming civilized home in Sussex, where, with his generous wife, herself a distinguished writer, he dispensed such enchanting hospitality. If ever there was a person who filled every moment of his day with good and valuable work it was John Keevil: his many friends had hoped that he would be spared for long to continue his life and to welcome and delight them, but, alas, his frame could not stand up to the strain, and we are all the poorer for his passing. Medicine can ill afford to lose such a devoted, honest, and faithful servant.

MAURICE MITMAN, M.B., F.R.C.P., D.P.H. D.M.R.E.

Dr. Maurice Mitman, medical superintendent of the River Hospitals, Dartford, died suddenly at his home at Dartford on December 13, 1957. He was 56 years of age.

Born on January 22, 1901, at Portsmouth, where he was educated at the grammar school, Maurice Mitman entered Guy's Hospital medical school in 1918, and from the first showed evidence of the brilliant professional career that was to follow. He qualified M.R.C.S., L.R.C.P. in 1923. Three years later he obtained the London degrees of M.B., B.S., with honours, and proceeded M.D. in 1928. He took the D.P.H. and the Cambridge D.M.R.E. in 1930. Elected a member of the Royal College of Physicians of London in 1927, he became a Fellow in 1945. After qualification he held house appointments at Guy's Hospital, including a period in the bacteriological laboratory, and at the London Skin Hospital, winning the Chesterfield medal of the London School of Dermatology in 1928. He acquired wide experience of general medicine and of the administrative aspects of social and preventive medicine in St. Charles's Hospital, Kensington, where he remained for three years. Thereafter his life work was devoted to the study of epidemiology and the control of acute infectious diseases, firstly at the North-eastern (now St. Ann's General) Hospital, Tottenham, then at the Eastern Hospital, Homerton, where, in 1936, he became medical superintendent at the early age of 35 years, and, finally, on the retirement of Dr. Archibald Cameron, he took charge of the L.C.C. River Hospitals, comprising Joyce Green, Orchard, and Long Reach hospitals, with a total capacity of nearly 2,000 beds.

Mitman was a prolific writer and in much demand as a lecturer in his specialty. In addition to various articles in the medical press he contributed to Rolleston and Moncrieff's *Diet in Health and Disease* (1939), to Conybeare's *Textbook of Medicine* (1940), and was joint author (with Dr. E. H. R. Harries) of *Clinical Practice in Infectious Diseases* (1945), a favourite with students and postgraduates which has run to five editions. As president of the Fever Group of the Society of Medical Officers of Health (1944) and of the Section of Epidemiology and Preventive Medicine of the Royal Society of Medicine (1955), he did much to enhance the authority and dignity of these offices. He was also president of the Kent Branch of the British Medical Association in 1950–1.

A memorial service for Dr. Mitman will be held at Joyce Green Hospital, Dartford, on Monday, January 13, at 3 p.m.

W. G. writes: For a year immediately before taking up the Eastern Hospital appointment Mitman was a divisional medical officer in the L.C.C. public health department at County Hall, where he acquired that intimate knowledge of committee work which was to stand him in good stead in the war period and perhaps especially after the inauguration of the National Health Service. The conversion of buildings designed for the care of infectious cases, primarily smallpox, into a first-class hospital dealing with civilian and Service patients—medical, surgical, and war injuries—was a major operation demanding his unremitting attention as fresh staffing and other problems continually arose, depending on the changes in the war situation. A special war-time unit was established at Joyce Green Hospital for the reception of Service personnel from the Netherlands, and in recognition of his services Mitman was appointed an officer of the Order of Orange-Nassau by the Queen of the Netherlands. He was conscientious to a fault and meticulous in practical details, and the task he undertook was not without its consequences, for his first attack of coronary disease occurred at the age of 51 years. Despite his indifferent health, he carried out his day-to-day duties with his accustomed acumen and energy. While smallpox was nominally his major preoccupation—he was official consultant in this specialty to the Ministry of Health—thanks to his diagnostic skill and administrative ability, the disease has never been a problem in London since he took charge, although it was imported from abroad many times in the war years and has been since, the last occasion being in July, 1957, when what might have been a serious epidemic was limited to six cases.

But it is perhaps in his social relations that Mitman was most outstanding, as he regarded patients and professional colleagues as his personal friends. In his private conversation and in committee deliberations he was knowledgeable, persuasive, and at all times reasonable; many who differed from his views had to admit that his arguments were soundly based and almost certainly would prove in the long run to be valid. He was whole-heartedly in favour of the medical administration of all services ministering to the health of the community, and from the first foretold inefficiency and extravagance from bureaucratic lay control. His prophecies have been amply fulfilled and are now widely, though not universally, admitted.

His interests were not exclusively confined to medicine; he was a keen collector of old glass and pictures, and played a sound game of bridge and chess. He was on the Dartford hospitals management committee for six years, being first chairman of the group medical committee, and had served on the governing body of the North-west Kent School of Technology since 1947. He will be greatly missed in the Dartford district, where he had made his home for the last twenty years, as well as in the wider professional sphere in which he made a much-loved name for himself. He was unmarried.

H. P. W. BARROW, C.B., C.M.G., D.S.O., O.B.E. M.R.C.S., D.P.H., D.T.M.

Major-General H. P. W. Barrow, formerly director of hygiene at the War Office and colonel commandant of the Royal Army Medical Corps, died at Brockenhurst, Hampshire, on December 20, 1957. He was 81 years of age.

Harold Percy Waller Barrow was born on June 30, 1876. Receiving his medical training at Guy's Hospital, he qualified M.R.C.S., L.R.C.P. in 1898, taking the Liverpool D.T.M. in 1908 and the Cambridge D.P.H. in the following year. Immediately after qualification he entered the R.A.M.C., and served in the South African war from 1900 to 1902, receiving the Queen's medal with three clasps and the King's medal with two clasps. In 1907–8 he was adjutant to the old Volunteers, and from 1908 to 1910 to the new Territorial Army. Attaining the rank of major in 1910, he was deputy assistant director-general of the Army Medical Services from 1914 to 1916, being promoted lieutenant-colonel in 1915. For his war services he was appointed C.M.G. in 1917 and O.B.E. in 1919, having been awarded the D.S.O. in 1918. He was also appointed an officer of the Belgian Order of the Crown in 1917, and to the second class Order of the Crown by the King of Siam in 1920. Sent to India in 1919 as director of hygiene and pathology at Army Headquarters, he held the appointment until 1922, when he became full colonel. From 1919 to 1923 he was an Honorary Surgeon to the Viceroy of India. Returning to England, he was deputy director of medical services in the Western Command in 1923–4, then becoming director of hygiene at the War Office, a position he held until he retired in 1930 with the rank of major-general. From 1926 to 1930 he was an Honorary Surgeon to the King, and he was appointed C.B. in 1929. After retiring from the Army Medical Services, he held the appointment of health officer at Antigua, in the British West Indies, for a few years, and was a member of the Federal Executive Council of the Leeward Islands and of the Executive Council of Antigua from 1930 to 1933. From 1941 to 1946 he was colonel commandant of the Royal Army Medical Corps, and from 1943 to 1952 a commissioner of the Royal Hospital, Chelsea. In 1938 he settled at Epsom, Surrey, and during the second world war he did useful work

in several capacities. Some four years ago he moved finally to Brockenhurst.

We are indebted to Sir ARTHUR MACNALTY for the following appreciation:

The Barrows as a family have a record of distinguished service in the British Army for several generations. Some have been more popular than others. Hence the Army jest that "there were good Barrows and bad Barrows." Major-General H. P. W. Barrow was emphatically one of the "good Barrows." He had a long period of service in the R.A.M.C. under five sovereigns, for he received his commission as a lieutenant in 1899 when Queen Victoria was on the throne and was colonel commandant of the R.A.M.C. in the reign of King George VI. In the many high posts which he held in his career he won the approval and esteem of his superiors and the affection and loyalty of his subordinates. He was on active service in three wars, and in the second world war he emerged from retirement to serve his country as a member of medical examining boards and for a time assisted the medical officer of health of the City of London in public health work.

My first meeting with Major Barrow, as he then was, occurred in 1914, when I was a medical inspector of the Local Government Board, seconded to the War Office for inspection of camps and hospitals and to promote co-operation in public health matters between the Army and the local authorities. As I had some difficulties in making my position clear to certain of the Army officers in charge of camps, I went round to the War Office, where I was received by Barrow, who was sitting on a camp-bed in his office eating sandwiches. "We work, eat, and sleep here so as to be ready for anything," he explained. On hearing my problem, he took me to see Major-General Sir William Macpherson ("Tiger Mac"), Deputy Director-General, A.M.S., who promised immediate action to smooth the path of the medical inspectors. This promise was fulfilled, and much wastage of man-power through recruits being sent to unsuitable camps was averted. Inevitably, other problems arose in my war work from time to time on which I had to confer with Barrow in his capacity as deputy assistant to the Director-General, A.M.S. He was always accessible and helpful, and we became friends.

Barrow was one of Sir William Macpherson's assistant editors for the twelve volumes of the *Medical History of the First World War, 1914–18*. To this *History* I contributed notes and information for the chapters on cerebrospinal fever and encephalitis lethargica, work which brought me into pleasant official relations with Barrow once more. In later days he took an interest in my planning of the *Official Medical History of the Second World War* and gave me the lessons of his experience with the earlier history.

For over ten years Barrow and his wife were neighbours and friends of ours at Epsom. One saw his well-knit military figure in the High Street, basket on arm, doing the daily shopping, or chatted with him while he pruned roses in his garden, for horticulture was his delight. He was also, I believe, an excellent bridge player. We greatly missed General and Mrs. Barrow when they left Epsom for Brockenhurst, in the New Forest. In an eventful life Barrow made no enemies. In war and in peace his merits and high integrity were conspicuous.

J. E. NEVINS, M.B.

Dr. J. E. Nevins, who was in general practice at Liverpool for many years, died on December 5 at the great age of 97.

The son of Dr. J. B. Nevins, a former president of the Liverpool Medical Institution who started his medical career as an apprentice, John Ernest Nevins received his medical education at the Liverpool Medical School before its incorporation into the university. Qualifying as M.R.C.S. and L.S.A. in 1886, he moved to University College, London, and Guy's Hospital, taking the London M.B., with honours, in the following year. He then served for several years as a ship surgeon, and then for five years from 1889 was personal physician to the Maharaja of Baroda, whom he accompanied on his travels and on his visits to the royal courts of Europe. These travels he recorded in his book, *Five Years at the Court of Baroda*.

Returning to England, Nevins began general practice in Liverpool, becoming visiting physician and, later, superintendent of the Brownlow Hill Hospital, where, with his sister, he endeared nimself to both staff and patients by his kindness to the poor and aged for twenty-six years. He was also consultant physician to the Highfield Infirmary and medical officer to the School for Deaf and Dumb. Nevins became vice-president of the Liverpool Medical Institution in 1920, and in 1944 was made an honorary life member after completing fifty years' membership. For his services as a teacher and examiner to the St. John Ambulance Association, he was appointed in 1930 a commander of the Venerable Order of St. John of Jerusalem. Retiring in 1937, he enjoyed wonderful health, physical agility, and mental clarity for twenty years until his death.

D. W. S. writes: Like his father before him, J. E. Nevins was a great philosopher and conversationalist, delighting all those privileged to know him by his wit, grace, and kindly good humour. Outliving most of his colleagues and friends, his last nine years were spent in a pleasant guest house, where his personality endeared him to everyone, young and old. Flouting senility himself, he was a great comfort to the aged, and by his personal discipline, method, observation, and consideration of others an inspiration to the young. With his white beard and black skullcap, Gladstone collar, and frock coat with satin facings, he had a patriarchal appearance. His knowledge and memory of the past were encyclopaedic and his interests of the present day many and varied. In spite of his great dignity, his delightful sense of the ridiculous enlivened many a meal-time, his repertory of comic songs and poems was immense, and his courtesy was of an age, alas, no more. Among his personal recollections were watching Lord Lister operate in Liverpool to demonstrate his carbolic spray, an excursion to London to see a case of healing by first intention, and an amputation being performed without an anaesthetic in the Royal Navy. A great Victorian, he saw a complete revolution of living habits and of medical science. His passing marks the end of a long chapter of Liverpool medical history, and the profession there has lost its oldest and most respected member.

T. R. GODDARD, M.R.C.S., L.R.C.P.

Dr. T. R. Goddard died at his home at Berkhamsted, Hertfordshire, on December 17, 1957, at the age of 63.

Thomas Richard Goddard was born on February 4, 1894. After serving in the first world war as a non-commissioned officer in the R.A.M.C., he studied medicine at University College Hospital, qualifying M.R.C.S., L.R.C.P. in 1925. Shortly afterwards he settled in general practice at Hemel Hempstead. He leaves a widow and one son.

Sir PHILIP MANSON-BAHR writes: I would like to put on record the services rendered by Dr. Tom Goddard in the Palestine campaign during the first world war. I first came into contact with him as a sergeant in the R.A.M.C. in July, 1917. At that time it had been decided to establish a field laboratory in close contact with the casualty clearing stations at Rafah immediately behind what was then the Gaza front. I had been put in charge of this field laboratory and relied upon Goddard to get the service established in record time. So efficient was he that our makeshift laboratory was in working order within two days and we were soon immersed in a sea of specimens of all kinds from the adjoining hospitals. The chief scourge was dysentery, mostly bacillary, and we were soon able to counter the prevailing impression that the *Entamoeba histolytica* reigned supreme. In actual fact we found this organism in about 3% of patients and then mostly in Egyptian and Indian

troops. Malaria was also much in evidence, and so was relapsing fever and occasionally typhus. It proved to be a great experience in tropical pathology and opened up avenues never to recur again. Goddard was invaluable. He prepared all the media for plating out dysentery stools and proved himself an expert in pathological technique.

There came a time in the winter of 1917–18 when the scare of cholera raised its head, and it was not long before Goddard had made himself familiar with the technique of isolating and identifying the *Vibrio cholerae*. Contacts and carriers were thereby isolated and the threatened epidemic came to an end; this was of critical importance because of the dependence of the Army to a great extent on well water. Then came the advance to Jerusalem and beyond through the intensely malarious country of the plains of Esdraelon. Allenby had been warned that this age-old enemy might prove the chief obstacle to success. The plan was envisaged of the formation of malaria diagnosis stations equipped with specially trained officers and laboratory personnel to diagnose and treat early infections of the benign and subtertian forms of malaria, each unit having at its disposal a general service wagon and four horses. For this purpose a malaria training establishment was set up at Deir Seneid with Goddard in charge of the laboratory arrangements. Here were assembled the necessary microscopes and specimens for a course which lasted six weeks in the early days of 1918. I owe it to Goddard that the scheme, which was a distinct innovation in wartime, proved a success. Six of these stations, manned by as many officers and 118 men, were equipped and took the field, and they proved their value in Allenby's last advance in September, 1918, when some of the units went forward with the cavalry past Damascus and on the road to Aleppo. They succeeded in diagnosing a very large number of cases of malaria, and by giving the patients early treatment with quinine saved the greater number from being evacuated down the line. It is not too much to say that without Goddard's efficient help it might have been a different story, because without doubt the greater part of the casualties in that historic advance were due to malaria and far exceeded the losses due to other causes. The experiences of war pathology and microscopical diagnosis acquired during his war service served Goddard very well when he came to take up his medical studies after demobilization. He became a most skilful and valuable doctor, and subsequently became a partner in a large practice in Hemel Hempstead.

L. E. NAPIER, C.I.E., F.R.C.P.

The obituary of Dr. L. E. Napier was printed in the *Journal* of December 28, 1957 (p. 1548).

Sir JOHN MEGAW writes: Napier's long and distinguished career as a medical research worker was closely associated with the Calcutta School of Tropical Medicine, which he joined as an original member of the staff in 1920, when he was selected to fill the post of special research worker on kala-azar. This post was one of three which had been endowed by the generosity of the Indian Tea, Jute-Mill, and Mining Associations in response to an appeal by Sir Leonard Rogers. It appears, therefore, that Napier's career was one of many that were founded on Sir Leonard's almost incredible success in realizing his great plan for creating in Calcutta a School of Tropical Medicine with an associated Institute of Hygiene and Hospital for Tropical Diseases. The staff of the combined institutions included nine full-time professors and six full-time special research workers with an ample staff of assistants. Napier's colleagues included such well-known workers as R. Knowles and B. W. Acton, R. N. Chopra, E. Muir, Asa C. Chandler, and R. O. A. Smith. In this environment Napier in 1924 made his most important discovery in collaboration with Knowles and Smith. The paper in which this was announced bears the title "On a Herpetomonas found in the Gut of the Sandfly *Phlebotomus argentipes*, fed on Kala-Azar Patients." The name "a Herpetomonas" was unhappy: it was chosen in deference to the criticism that the identification of the organisms as herpetomonad stages of *Leishmania donovani* was not absolute. In view of all the circumstances there could have been little doubt regarding the identity of the organism or that the inclusion of the name *L. donovani*, even if qualified by prefixing the word "probably," would have prevented the misunderstandings which arose. This important discovery did not result from a stroke of luck. By a careful survey the workers at the School had found that *P. argentipes*, alone among the blood-sucking arthropods of Calcutta, had a distribution corresponding with that of the cases of kala-azar, and that a similar agreement between the distribution of kala-azar and of the sandfly appeared to exist in the rest of India.

None of the three workers directly concerned in this discovery thought of making any claim to special credit for his work; indeed, all of them insisted on sharing the recognition with Acton on account of the fruitful suggestions received from him.

The kala-azar department soon became the world's leading centre for study of the disease. Eighteen beds were reserved in the hospital for treatment of patients, and a large out-patient department was maintained at which about 1,000 patients were treated yearly. The introduction of improved drugs for treatment was greatly helped by Napier's maintenance of a close liaison with the leading manufacturers. The well-known "aldehyde" treatment was introduced and was a great help in diagnosis. Napier in due course became director and professor of tropical medicine at the school; he filled both of these posts with great credit.

On his retirement after the war he spent some time in the U.S.A., and while there he completed his excellent book on tropical medicine. This was published in 1946 and would certainly have had great success but for the grave fault of being too expensive. Since 1946 he has been a regular contributor of excellent abstracts of papers on kala-azar. The awards of C.I.E. and F.R.C.P. indicate the recognition of his valuable services by the Government of India and the medical profession. He had the good fortune to enjoy a long and happy married life, and the sympathy of his wide circle of friends will go out to Mrs. Napier.

In the obituary of Dr. Trevor Griffiths (October 5, 1957. p. 832) we omitted to mention that Dr. Griffiths proceeded to the degree of M.D. at the University of Wales in 1957.

Medical Notes in Parliament

Accidents in the Home

Before the Commons separated for Christmas they were led by Mrs. JEAN MANN (Coatbridge and Airdrie, Lab.) and the Home Safety Group—an all-party organization—to take a look at accidents in the home and what might be done to reduce their numbers (December 19).

Dr. DONALD JOHNSON (Carlisle, Con.), who is joint chairman of the group, made a novel contribution to this discussion. Using the pattern of a Sunday newspaper quiz on whether one was "the perfect lover," with marks for the various qualifications listed, he examined the arrangements in his own home, and reached in the end "a great sense of inadequacy" for holding office in the group. Dr. Johnson told the House that he had a family of three, whose ages ranged from 26 to 2½ years. Thus, except for a comparatively short interval, there had always been a child in the home, and a continuous consciousness of accidents to children.

These were the tests he applied, and his answers. *Open fires:* In his home they had an open fire with a very inadequate guard. To-day was the first time his wife had been able to tell him that she had even seen the proper kind of

safety fireguard in their shops. Marks—nil. *Electric fires:* They were still using the old type. Marks—none recorded. *Matches:* They had had several displays of pyrotechnics in which his young daughter had been concerned, fortunately without ill results. Marks—again none recorded. *Pyjamas:* There at least he scored. He could not imagine any parents with the obvious knowledge at their disposal clothing small girls in anything else. *Poisons:* Their arrangements were slightly rough and ready, the only bottle of tablets in the house being put in the only place to which a child could not climb, on top of the wardrobe. He doubted the efficacy of locked cupboards. Marks—here he gave himself a mark. This "shocking example" in his own home led him to speculate. He thought himself typical of a large number of parents. How were they to be educated in these matters? "Our great trouble is that we put our homes together, we get our routine, and we are resistant to change." It would be an excellent thing if home safety education could be part of antenatal clinic training and advice. Dr. Johnson also mentioned deaths from suffocation due to overlying in bed or a cat lying on the baby's pram—things that would not occur to a young mother unless she was reminded. Finally, in the context of the increasing use of medicine in tablet form, he spoke of the carelessness with which tablets were left about, and suggested that a label of special colour should be put on poisonous and semi-poisonous tablets when they were dispensed, plus a warning to parents to keep them out of reach of children.

Flame-resistant Fabrics

This debate, taking place within a week of Christmas, ranged from the dangers of naked lights and party dresses for the young to polished floors for the old. On the latter Mrs. MANN, for example, observed, "It seems to me that the propensity of my sex to insist on highly polished floors is just as dangerous as huge fires without guards." On the former Mrs. P. P. MCLAUGHLIN (Belfast, West, U.U.), who shared her regret that progress during the past year had been slow, emphasized the need for publicity and education to make the housewife demand non-flammable material when the standard was produced. Mr. H. MARQUAND (Middlesbrough, East, Lab.) was disappointed on this score too, but unable to pinpoint the reason for it. Commenting on the time and cost of treating burns, he urged the Government, simply as a matter of money, to set alongside a little expenditure on educating the public in the precautions to take and the sort of material to buy the much greater saving there would be in the Health Service. He emphasized what others had said in seeking an extension of the Government grant to the Royal Society for the Prevention of Accidents for its work on home safety.

Mr. J. E. S. SIMON, Joint Under Secretary at the Home Office, offered them no hope on this. When the grant was renewed three years ago, he said, it was made plain that it was for three years only. If it was not renewed, that did not mean that the campaign need fail. The British Standards Institution inquiry had shown that nearly all lightweight fabrics made potentially dangerous garments. Research and development in the flame-proofing of fabrics was progressing at the British Cotton Industrial Research Association Institute, and by a number of commercial interests. To facilitate the establishment of a British Standard of flame-resistant fabric for apparel the Board of Trade had undertaken to issue new regulations under the Fabrics (Misdescription) Act, 1913. For the effective enforcement of proper fireguards there must be inspection, and in the domestic sphere that was not acceptable. The answer here was education. It was in the growth of home safety committees that the major advance was to be looked for. The formation of the 100th had been announced, but that covered only a small part of the country. Local authorities were not sufficiently aware of their powers under the Health Service Act to help in home safety measures. The Minister of Health intended to send out a circular early in the new year; it would urge local authorities to take the initiative in establishing home safety committees; draw attention to the advice health visitors could give to parents and old people, and the educational work that could be undertaken at welfare clinics and by voluntary organizations; and contain a useful appendix on burns and scalds, and their prevention. Hospitals would be asked to supply statistical information to medical officers of health about the incidence of serious home accidents, in the form of quarterly figures giving age, sex, nature of accident, and so on.

Abortion

Mrs. LENA JEGER (Holborn and St. Pancras South, Lab.) asked the Home Secretary what consideration he had given to the report of the inter-departmental committee on abortion which was submitted in 1939; and what action he proposed to take to implement the recommendations of the committee. Mr. R. A. BUTLER stated in a reply on December 20 that so far as the Home Office was concerned the committee's principal recommendation was that, subject to certain safeguards, the law should be amended to make it clear that a doctor would not commit an offence if, in good faith, he terminated a pregnancy which he considered likely to endanger the mother's life or seriously to impair her health. Legislation for this purpose would be highly controversial, and he had no reason to think that there was any practical need for it. He did not propose to introduce legislation to implement certain minor recommendations designed to facilitate prosecutions for criminal abortion. The recommendation that the Poisons Board should be consulted on the desirability of placing further restrictions on the sale of certain abortifacients was implemented in June, 1939; the board did not recommend any action. The recommendation that a circular should be sent to coroners about the importance of the vigilant investigation of deaths resulting from abortion was implemented in October, 1939.

Mrs. JEGER asked the Minister of Health what action he proposed to take in accordance with the recommendations of the committee. Mr. RICHARD THOMPSON, Parliamentary Secretary, stated that the recommendations were considered at the time but action was deferred by the war. Such recommendations as were the Minister's concern had been largely implemented since the committee reported by the improvements in the social and economic factors relating to childbirth and the availability of free maternity services under the Health Service. He was, however, keeping under constant review the measures needed to reduce avoidable maternal deaths, including those due to abortion.

Doctors' Car Parking Difficulties

Sir WAVELL WAKEFIELD (St. Marylebone, Con.) asked the Home Secretary on December 19 if he was aware that on November 22, about noon, Dr. B. Rogol was urgently called to visit the National Heart Hospital in Westmoreland Street, and, having tried without success to park his car for a considerable time, found a space in New Cavendish Street without realizing it was too close to a pedestrian crossing to leave the car; and that when he came out of the hospital 10 minutes later for further urgent visits he found his car had been driven away by the police, even though they knew it was a doctor's car. Sir Wavell Wakefield asked that instructions should be issued to the police not to take away doctors' cars in such circumstances.

Mr. BUTLER said he was aware of the incident mentioned, but as there was a possibility of court proceedings he could not comment upon it. On the general question, while the difficulties experienced by doctors in finding parking space in central London were appreciated and the police gave all the help they could, they must be free to remove a doctor's car in an appropriate case when the owner could not be traced. It would obviate the need for removal in most cases if doctors having to park in a busy area were to adopt the practice recommended by the Commissioner of Police of leaving a note on the windscreen giving the owner's name and the place where he could be found.

Poliomyelitis Vaccination

Mr. S. P. VIANT (Willesden, West, Lab.) asked to what extent the adverse effects which primary vaccination might have on the foetus, if done during the first three months of pregnancy, might also occur with anti-poliomyelitis vaccine. Mr. THOMPSON said he was advised that there was no good evidence of any adverse effects on the foetus, apart from the extremely remote risk of generalized infection associated with smallpox vaccination; and that even this risk was not present in the case of poliomyelitis vaccination.

Consultants' Salaries Per Bed

Mr. SOMERVILLE HASTINGS (Barking, Lab.) wanted to know what was the average annual cost per in-patient bed of the services of medical consultants in each of the 14 hospital boards.

Mr. D. WALKER-SMITH gave him these figures for the financial year 1956–7:

Regional Board Area	Average Cost £
1. Newcastle-upon-Tyne	41·5
2. Leeds	28·4
3. Sheffield	33·6
4. East Anglian	36·5
5. N.W. Metropolitan	45·8
6. N.E. ,,	40·4
7. S.E. ,,	43·6
8. S.W. ,,	30·3
9. Oxford	36·9
10. South-Western	30·3
11. Wales	33·2
12. Birmingham	34·9
13. Manchester	28·5
14. Liverpool	33·6

Hospital Services and Practice

Dr. DONALD JOHNSON (Carlisle, Con.) asked for the total number of qualified doctors employed in the Health Service; and the numbers employed in each of the three branches of the Service, local authority, hospitals, and executive councils, respectively. Mr. WALKER-SMITH stated that such figures were not collected for the Service as a whole. The approximate numbers employed in the hospital service and in general practice under the Service were: hospital service (excluding honorary staff), 17,300 at the end of 1956; general practice (including assistants), 22,000 in January, 1957. These figures were not mutually exclusive, as many doctors were employed both in the hospital service and in general practice. The latest available figure for local authorities related to 1954, when 2,100 doctors were employed by local authorities generally: the number employed in the provision of local health services under the Health Service was not available.

Arsenite Sprays

Mr. HASTINGS asked the Minister of Agriculture, Fisheries, and Food how many cases of poisoning had been notified in those engaged in agricultural spraying with sodium and potassium arsenite in the last five years; and in how many cases spraying with these substances had been regarded as a causative agent in cases of dermatitis and cancer. Mr. J. GODBER, the Parliamentary Secretary, said the Ministry knew of one case of a person taken ill after being engaged in spraying with alkaline arsenites; and of one occurrence in which arsenical poisoning was diagnosed in seven persons who had picked potatoes very shortly after the haulms had been sprayed with arsenites. He knew of no case in which spraying with these substances had been regarded as a causative agent of dermatitis or cancer.

He also told Mr. Hastings that the Ministry had no information about how long after the spraying of the haulms of the potato plant with arsenical compounds this element had been detected in the soil. Potato plants, like all plants, might absorb arsenic in minute quantities, and some tubers of potato crops sprayed with arsenical haulm-killers had been found to contain arsenic, nearly always in the peel only, but in quantities below the limit recommended by the Food Standards Committee.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 14** (No. 50) and corresponding week 1956.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire	1956 Eng. & Wales	1956 Lond.	1956 Scot.	1956 N. Ire.	1956 Eire
Diphtheria	3	1	2	0	3	6	0	6	0	4
Dysentery	669	121	128	12	2	808	50	245	6	
Encephalitis, acute	0	0		0		5	1		0	
Enteric fever:										
Typhoid	0	0	1	0		1	0	0	0	1
Paratyphoid	11	0	1 (B)	0	2(B)	2	0	3 (B)	0	
Food-poisoning	128	5	21	1		319	29	22	0	
Infective enteritis or diarrhoea under 2 years				5	25				12	7
Measles *	2,450	40	49	44	8	6,493	397	542	189	161
Meningococcal infection	34	1	5	0	1	39	3	14	1	1
Ophthalmia neonatorum	19	1	1	0		23	0	10	1	
Pneumonia †	778	52	354	9	21	550	42	264	4	2
Poliomyelitis, acute:										
Paralytic	53	0	4	0	4	49	8	4	0	9
Non-paralytic	18	0				24	4			
Puerperal fever §	233	62	2	2		188	18	10	3	
Scarlet fever	794	50	62	20	17	766	56	70	18	23
Tuberculosis:										
Respiratory	507	58	102	22		578	64	134	27	
Non-respiratory	45	2	14	1		88	4	16	6	
Whooping-cough	504	23	38	3	6	1,979	101	354	16	35

DEATHS in Great Towns	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire	1956 Eng. & Wales	1956 Lond.	1956 Scot.	1956 N. Ire.	1956 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	0	1	2	7	0	1	0	0
Influenza	99	16	2		6	12	1	1	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	566	105	24	20	16	279	40	14	11	6
Poliomyelitis, acute	7	0		0	0	2	1			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	96	16	11	0	7	59	10	10	0	4
Non-respiratory		4	0	0	0		0	1	0	1
Whooping-cough	0	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	257	35	26	16	10	225	26	17	8	12
Deaths (excluding stillbirths)	7,448	1212	711	124	172	5,316	769	529	220	150
LIVE BIRTHS	7,406	1089	943	227	291	7,108	1059	895	115	355
STILLBIRTHS	187	28	17			183	20	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Expectation of Life

The expectation of life in England and Wales based on 1956 mortality experience is at birth 67.76 years for boys and 73.30 for girls. At age 65 it is 11.85 years for men and 14.88 for women.—*Registrar-General's Quarterly Return for England and Wales*, Third Quarter, 1956, H.M.S.O.

Scotland in 1956

The infant mortality rate in 1956 was the lowest recorded for Scotland (28.6 per 1,000 live births), and the death rate for tuberculosis again fell (to 16 per 100,000 population from 19 in 1955). The maternal mortality rate of 0.5 per 1,000 live and still births was the same as in 1955, and the general death rate at 12 per 1,000 population has been the same for the last three years.

The main causes of death with an increasing incidence over the last decade were malignant neoplasms (209 per 100,000 population), vascular lesions of the nervous system (188), and arteriosclerosis and degenerative heart disease (358).

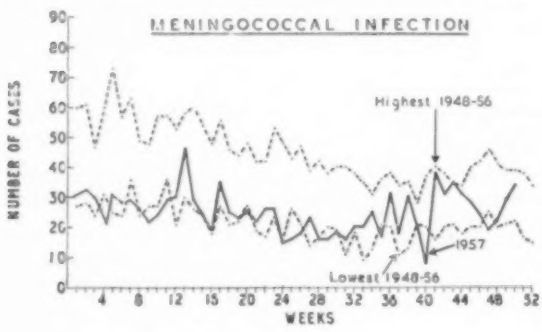
Among infectious diseases causing deaths were tuberculosis 801, syphilis 88, meningococcal infections 27, whooping-cough 14, measles 10, acute poliomyelitis 9, dysentery 3, typhoid 2, scarlet fever 2, and diphtheria 2. Bronchitis caused 2,077 deaths, pneumonia 1,916, and influenza 262. The number of deaths from suicide, 403, was the highest since the war; the number of deaths from motor vehicle accidents, 558, was slightly lower than in 1955 and in 1953, but higher than in all other years since the war.

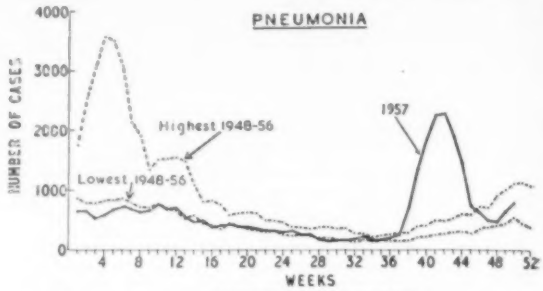
The birth rate was 18.5 per 1,000 population, which was 0.5 higher than in 1955, and 0.7 above the average for 1951–5. The number of marriages in Scotland was also unusually high in 1956. The rate of 8.5 per thousand population was 0.1 above that for 1955, and 1.5 above the rates of 50 years ago.

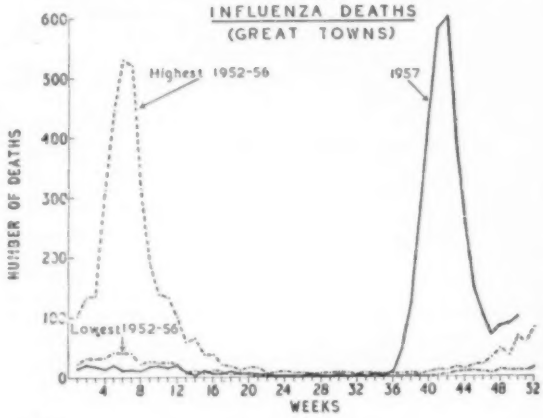
Deaths under anaesthetics numbered 168. Of the 165 cases in which the anaesthetic was stated, thiopentone, usually in combination with another anaesthetic agent, was administered in 91 cases. Nitrous oxide alone was administered in 24 cases.—*Annual Report of the Registrar-General for Scotland*, 1956, No. 102, H.M.S.O. 15s.

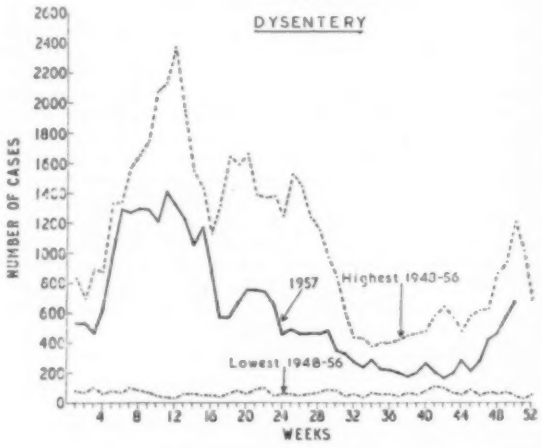
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the years 1948–56 (influenza, 1952–6) are shown thus - - - - - -, the figures for 1957 thus ————. Except for the curves showing notifications in 1957, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The largest rises in the notifications of infectious diseases in England and Wales during the week ending December 14 were 236 for measles, from 2,214 to 2,450, 129 for acute pneumonia, from 649 to 778, 93 for dysentery, from 576 to 669, and 71 for scarlet fever, from 723 to 794; the only large fall was 71 for whooping-cough, from 575 to 504.

The largest increases in the incidence of measles were 75 in Glamorganshire, from 218 to 293, and 70 in Hertfordshire, from 113 to 183; the largest decrease was 34 in Staffordshire, from 68 to 34. The local trends of whooping-cough and scarlet fever showed only small fluctuations. 3 cases of diphtheria were notified, being 2 more than in the preceding week. A small rise in the incidence of acute pneumonia occurred throughout the country.

9 of the 11 cases of paratyphoid fever were notified in South Westmorland R.D.; 6 cases were notified in this area in the preceding week.

The notifications of acute poliomyelitis numbered 71, and these were 8 fewer for paralytic and 2 fewer for non-

paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 14 (Bradford C.B. 8, Leeds C.B. 3, Rawmarsh U.D. 2), Surrey 7 (Surbiton M.B. 2, Wimbledon M.B. 2), Kent 6 (Margate M.B. 3), and Berkshire 5.

The largest centres of dysentery were Lancashire 158 (Eccles M.B. 35, Liverpool C.B. 31, Preston R.D. 26, Salford C.B. 16, Whiston R.D. 11), London 121 (Islington 33, Stoke Newington 20, Fulham 18, Finsbury 17, Hammersmith 15), Yorkshire West Riding 114 (Bradford C.B. 29, Sheffield C.B. 21, Holmfirth U.D. 11), Suffolk 44 (Thingoe R.D. 44), Hertfordshire 31 (St. Albans R.D. 31), and Surrey 27 (Reigate M.B. 16).

Medical News

Chair of Orthopaedic Surgery, Edinburgh.—Mr. J. I. P. JAMES, assistant director of the Institute of Orthopaedics (London University), has been appointed to the chair of orthopaedic surgery at Edinburgh University. He succeeds Sir WALTER MERCER and is expected to take up his appointment in April. Mr. James qualified in 1938 from University College Hospital, London, proceeding M.B., B.S.(Lond.), F.R.C.S.(Eng.) in 1940. Two years later he took the degree of M.S. During the war Mr. James served with the R.A.M.C., ending as lieutenant-colonel. In 1947–8 he held a Rockefeller travelling fellowship in the United States. Besides being assistant director of the Institute of Orthopaedics Mr. James is also an honorary surgeon to the Royal National Orthopaedic Hospital.

Commonwealth Medical Advisory Bureau.—Dr. R. A. PALLISTER has taken up his duties at B.M.A. House as director of the Commonwealth Medical Advisory Bureau and of the International Medical Visitors' Bureau. He was formerly senior physician to the Government of the Federation of Malaya. In both these posts he succeeds Brigadier H. A. SANDIFORD, who has retired under the age limit. Brigadier Sandiford was appointed in 1948 when the Association founded the Commonwealth (then Empire) Medical Advisory Bureau. At the Bureau's Christmas "At Home" on December 19, Mr. A. M. A. MOORE, chairman of the committee of management, paid a warm tribute to Brigadier and Mrs. Sandiford's devoted work for overseas medical visitors during the past 10 years.

Medical Fellowships for 1958–9.—The Medical Research Council invites applications for the following series of fellowships for the academic year 1958–9 (in each case the closing date for applications is given in parentheses): (*a*) Rockefeller travelling fellowships in medicine (March 1); (*b*) Dorothy Temple Cross research fellowships in tuberculosis (March 1); (*c*) Alexander Pigott Wernher memorial travelling fellowships in ophthalmology and otology (March 31); (*d*) fellowships in clinical research (March 1); and (*e*) French Government exchange scholarships in medical science (March 31). The fellowships in clinical research are intended for medical graduates wishing to prepare themselves for a career in clinical research and are tenable at centres in the United Kingdom. Full details of these and the other fellowships listed, together with application forms, may be obtained from the Secretary of the Medical Research Council, 38, Old Queen Street, London, S.W.1.

U.S. Public Health Service Fellowships.—The Medical Research Council has been invited by the United States Public Health Service to nominate candidates for the Service's travelling fellowships. The final selection of fellows will be made by the National Institutes of Health, Bethesda. The purpose of these fellowships is to enable highly qualified foreign scientists to carry out research in medical and biological laboratories in the United States. The usual period of tenure will be one year. Applications should be lodged by March 1 with the Secretary of the Medical Research Council, 38, Old Queen Street, London, S.W.1, from whom may be obtained further details.

Smoke Control Areas.—Five orders for the creation of smoke control areas under the Clean Air Act, 1956, were confirmed recently by the Minister of Housing and Local Government. The orders were made by Bolton, Denton (Lancs), Hayes and Harlington (Middlesex), Ossett (Yorks), and West Bromwich local authorities, and they affect a total of 380 acres (154 hectares). The only other order which has been confirmed under the Clean Air Act dealt with the city centre of Liverpool. All the orders come into operation this year. Only in the case of West Bromwich were objections lodged, main ones being that smoke nuisance from industries and the railways should be reduced before householders were required to burn smokeless fuel; that coke fumes in houses with a down draught were dangerous; and that the cost of replacing or adapting fireplaces to burn smokeless fuels would cause financial hardship. In confirming the West Bromwich Order the Minister postponed the date for its operation until November 1, 1958, to allow time for alterations to fireplaces and to enable powers under the Clean Air Act for controlling smoke from industry and the railways to be brought fully into force.

Course on Nuclear Protection.—On behalf of W.H.O., the United Kingdom Atomic Energy Authority is holding a course at Oxford this month on the public health aspects of nuclear protection. The course, which lasts from January 6 to 17, is being attended by public health administrators, industrial medical officers, and sanitary engineers from 20 countries in W.H.O.'s European Region.

Colyer Medal.—The Faculty of Dental Surgery of the Royal College of Surgeons has conferred its Colyer gold medal on Lord NUFFIELD in appreciation, particularly, of his founding the Nuffield research chair in dental science at the college.

Asthma as a Social Problem.—At its second international conference, held in Lisbon in the autumn, the International Association for Asthmology (Interasma) debated "The Social Problem of Asthma." Interasma is an association of national societies concerned with allergic disorders. The congress concluded that bronchial asthma was increasing in all countries, that present methods of treatment were almost exclusively symptomatic, and that better results would be obtained by instituting in each country "a rational and specialized programme of assistance to asthmatic patients." Recommendations based on these findings were forwarded to the World Health Organization and other agencies.

Royal Society of Health.—The following have been made fellows: Dr. M. E. M. HERFORD, appointed factory doctor for the Slough, Windsor, and Eton Districts, Dr. T. L. HUGHES, S.A.M.O., Liverpool Regional Hospital Board, Miss ELEANOR J. MERRY, general superintendent, Queen's Institute of District Nursing; Dr. T. E. ROBERTS, M.O.H., Portsmouth, and Dr. JOSEPH WEINSTEIN, district health officer, New York City Department of Health.

Cambridge University.—The appointments are announced of Dr. LESLIE COLE as dean of the Postgraduate Medical School and of Dr. DIANA BRINKLEY as clinical research assistant to the Regius Professor of Physic (see *Journal*, December 7, p. 1379). Dr. J. W. MILLEN has been appointed reader in anatomy, and Dr. H. F. GRUNDY lecturer in the department of pharmacology.

Bristol University.—Dr. D. W. BARRITT has been appointed lecturer in medicine and Dr. D. R. COLES a research fellow in the department of medicine.

Leeds University.—Dr. C. C. D. CHANDLER has been appointed lecturer in the department of anaesthetics.

Mr. A. L. d'Abreu, reader in thoracic surgery at Birmingham University, is spending a month lecturing in Peru under British Council auspices.

COMING EVENTS

Institute of Dermatology.—Semi-permanent exhibition on "The Normal Epidermis and Some Precancerous Conditions," January 1–17.

Radio.—"Psychiatry and Medicine" in the B.B.C. series "The Frontiers of Psychiatry," January 8, 8.50 p.m. in the Third Programme.

Watson Smith Lecture.—Dr. M. S. THOMSON will lecture on "Some Aspects of Industrial Dermatitis" on January 9 at 5 p.m. at the Royal College of Physicians of London.

Juvenile Delinquency.—Course of twelve lectures (6.30 p.m., January 10 to March 28) on the psychological, psychiatric, social and administrative aspects. Details from the Institute for the Study and Treatment of Delinquency, 8, Bourdon Street, Davies Street, London, W.1.

Goulstonian Lectures.—At the Royal College of Physicians of London on January 14 and 16, at 5 p.m., Dr. A. G. LEATHAM will lecture on "Auscultation of the Heart."

NEW ISSUES

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Pharmacology and Chemotherapy.—Issued quarterly (£4 4s. annually). The new issue, Vol. 12, No. 4, includes:

SUSCEPTIBILITY OF CERTAIN ENZYMES OF THE CENTRAL NERVOUS SYSTEM TO TETRODOTOXIN. K. Kuriaki and H. Nagano.
A METHOD OF ESTIMATING HISTAMINE IN PLASMA. H. M. Adam, D. C. Hardwick, and K. E. V. Spencer.
THE EFFECT OF LYSERGIC ACID DIETHYLAMIDE, 5-HYDROXYTRYPTAMINE, AND RELATED COMPOUNDS ON THE LIVER FLUKE, FASCIOLA HEPATICA. T. E. Mansour.
THE ACTION OF 5-HYDROXYTRYPTAMINE AND SOME OF ITS ANTAGONISTS ON THE UMBILICAL VESSELS OF THE HUMAN PLACENTA. A. Åström and U. Samelius.
THE ADRENALINE AND NORADRENALINE CONTENT OF THE ADRENAL GLAND OF THE CAT FOLLOWING DEPLETION BY ACETYLCHOLINE. K. R. Butterworth and Monica Mann.
THE RELEASE OF ADRENALINE AND NORADRENALINE FROM THE ADRENAL GLAND OF THE CAT BY ACETYLCHOLINE. K. R. Butterworth and Monica Mann.
A COMPARISON OF THE LOCAL EFFECTS OF VARIOUS INTRAMUSCULAR INJECTIONS IN THE RAT. G. E. Paget and H. McG. Scott.
THE ANTITUBERCULOUS ACTIVITY OF ETHYL THIOLESTERS, WITH PARTICULAR REFERENCE TO DIETHYL DITHIOLISOPHTHALATE. G. E. Davies and G. W. Driver.
PROTECTION AGAINST THE LETHAL EFFECTS OF ORGANOPHOSPHATES BY PYRIDINE-2-ALDOXIME METHIODIDE. F. Hobbiger.
PHARMACOLOGICAL PROPERTIES OF ESTERS OF 1-ALKYL-2-HYDROXYALKYLPYRROLIDINE AND THEIR QUATERNARY DERIVATIVES. P. Acred, E. M. Atkins, J. G. Bainbridge, D. M. Brown, R. M. Quinton, and D. Turner.
ACTION OF ANAPHYLACTIC SHOCK AND ANAPHYLATOXIN ON MAST CELLS AND HISTAMINE IN RATS. Ivan Mota.
THE EFFECTS OF MECAMYLAMINE IN THE CAT AS MODIFIED BY THE ADMINISTRATION OF CARBON DIOXIDE. J. P. Payne and G. G. Rowe.
THE EFFECTS OF NICOTINE, HEXAMETHONIUM AND ETHANOL ON THE SECRETION OF THE ANTIDIURETIC AND OXYTOCIC HORMONES OF THE RAT. G. W. Bisset and J. M. Walker.
THE TOXICITY OF DIAMINODIPHENOXYALKANES. L. G. Goodwin, W. H. G. Richards, and V. Udall.
THE EFFECT OF HUMAN PLASMA ON THE GLUCOSE UPTAKE OF THE RAT DIAPHRAGM BEFORE AND AFTER ADMINISTRATION OF CARBUTAMIDE. Ranita Alman and R. D. Kulkarni.
THE EFFECT OF METHYLPENTYNOL IN MAN. S. E. Dicker and Hannah Steinberg.
THE ANTIDIURETIC ACTION OF 5-HYDROXYTRYPTAMINE IN CATS IN RELATION TO THE PRODUCTION OF CERTAIN CHEMOREFLEXES. F. N. Fastier and Hendrieka Waal.
THE ETHYLENEIMINIUM ION AS THE ACTIVE SPECIES IN 2-HALOALKYLAMINE COMPOUNDS. J. D. P. Graham.
THE ANTAGONISM OF THE VASCULAR EFFECTS OF 5-HYDROXYTRYPTAMINE BY BOL 148 AND SODIUM SALICYLATE IN THE HUMAN SUBJECT. W. E. Glover, R. J. Marshall, and R. F. Whelan.
THE EFFECTS OF ANTICHOLINESTERASES ON THE BRONCHIOLES AND PULMONARY BLOOD VESSELS IN ISOLATED PERFUSED LUNGS OF THE DOG. M. de Burgh Daly.
THE OXIDATION OF CYSTAMINE AND HOMOCYSTAMINE BY MAMMALIAN ENZYMES. Bernadette Bergeret, and H. Blaschko.
METABOLIC AND OTHER EFFECTS OF RESERPINE UPON SMOOTH AND SKELETAL MUSCLE. C. N. Gillis and J. J. Lewis.
DETECTION AND MEASUREMENT OF ANTAGONISM TO FOLIC ACID. H. O. J. Collier, J. J. Grimshaw, and Patricia L. Huskinson.
INTRAVENTRICULAR ADMINISTRATION OF RESERPINE AND ITS METABOLITES TO CONSCIOUS CATS. S. R. Dasgupta and T. J. Haley.
THE CONCENTRATION OF ADRENALINE IN THE PLASMA OF RABBITS TREATED WITH RESERPINE. E. Muscholl and Marthe Vogt.
THE EFFECT OF DIISOPROPYL FLUOROPHOSPHONATE ON THE SENSITIVITY OF RATS TO CENTRALLY ACTING DRUGS. Brenda J. Bayliss, J. Elkes, Sheila G. Spanner, and A. Todrick.
INDEX TO VOLUME 12.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 6

MARLBOROUGH DAY HOSPITAL.—8.15 p.m., Dr. S. T. Hayward: On Being Ill in a Mental Hospital.

Tuesday, January 7

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Mr. B. E. D. Cooke: Disorders of Buccal Mucosa.
LONDON UNIVERSITY.—At Beatstead Lecture Theatre, London Hospital Medical College, Turner Street, E., 5.30 p.m., special university lecture in pharmacology by Dr. E. Jacobsen (Copenhagen): Pharmacological Classification of Central Nervous Depressants.

Wednesday, January 8

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: Biochemistry of Hormones. (1) Steroids.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Howard Nicholson: Chronic Pulmonary Suppuration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. J. F. Loutit: Successful Transplantation of Homologous and Heterologous Tissue in the Experimental Mouse.
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION. PSYCHOTHERAPY AND SOCIAL PSYCHIATRY SECTION.—At 11, Chandos Street, W., 8 p.m., Mrs. McDougall (London School of Economics): Role of the Psychiatric Social Worker in the Mental Hospital.

Thursday, January 9

GLASGOW UNIVERSITY AND ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—At Royal Faculty of Physicians and Surgeons, 3 p.m., conference on obstetrics and gynaecology. Professor I. Donald, Dr. R. A. Tennent, and Dr. J. S. Barr: Imminent Eclampsia.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Lord Evans: Significant Hypertension.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Watson Smith Lecture by Dr. M. S. Thomson: Some Aspects of Industrial Dermatitis.
ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Binocular Vision in Refraction Work.

Friday, January 10

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. S. C. Gold: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m. Dr. F. H. Scadding: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 3.30 p.m., clinical discussion for general practitioners by Mr. A. Radcliffe: Hoarseness. (2) 5.30 p.m., Mr. A. Radcliffe: clinical demonstration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. J. C. Barrett: Multiple Primary Malignant Neoplasm.
ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., dissertation by Mr. J. G. Turnbull: Disseminated Sclerosis.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—C. W. Gordon, M.B., Ch.B., D.P.H., Dr.P.H., Senior Administrative Medical Officer of the Board.

BRADSHAW, J. P. P., M.D., M.R.C.P., Assistant Neurologist (Consultant Grade) to Royal Infirmary and Royal Hospital at Sheffield.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Rajeswari Sathasivam, M.B., B.S., M.R.C.P., D.C.H., House-physician; Priscilla A. Ridge, M.B., B.S., House-surgeon to Orthopaedic and Plastic Departments; R. G. Williams, M.B., B.S., F.R.C.S., D.L.O., Senior Registrar to Ear, Nose, and Throat Department; B. G. Wells, M.D., M.R.C.P., Part-time Medical Officer to Cardiothoracic Unit; M. A. Birnstingl, M.B., B.S., F.R.C.S., Surgical Out-patient Assistant; E. Goldblatt, M.B., B.Ch., D.C.H., Assistant Medical Registrar; Pamela M. Hellings, M.B., Ch.B., F.F.A. R.C.S., D.A., Senior Registrar in Anaesthetics; Charlotte Grantz, M.D., House-physician; I. Yentis, M.D., F.F.R., M.R.C.P., D.M.R.D., Senior Registrar in Radiology (to be shared with University College Hospital); I. W. Broomhead, M.B., B.Chir., F.R.C.S., Part-time Senior Registrar in Plastic Surgery (to be shared with St Thomas's Hospital); H. L. Utian, M.B., B.Ch., and J. W. Scopes, M.B., B.S., House-physicians; G. S. Cameron, M.D., B.Sc.(Med.), F.R.C.S.C., and J. G. Smith, M.B., B.S., House-surgeons; Mrs. Katharine M. Dormandy, M.B., B.S., M.R.C.P., Registrar in Clinical Pathology.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Anderson.—On December 8, 1957, at Bournemouth, Hants, Robert Anderson, L.R.C.P.&S.Ed., L.R.F.P.S., aged 76.
Bak.—On December 6, 1957, at The National Temperance Hospital, Dora Bak, M.D., aged 68.
Carey.—On December 15, 1957, Richard Stocker Carey, O.B.E., M.R.C.S., L.R.C.P., of 502, Bath Road, Brislington, Bristol.
Colmer.—On December 15, 1957, Cecil Colmer, M.B., B.S., of The Shrubbery, Barnfield Road, Exeter, aged 76.
Finlay.—On December 15, 1957, in a nursing-home, Hove, Sussex, James Donald Finlay, M.B., C.M., of 2, Withdean Hall, Brighton, Sussex, aged 86.
Gauld.—On December 15, 1957, George Ogg Gauld, T.D., M.R.C.S., L.R.C.P., of Audley, Staffs, aged 53.
Hindhaugh.—On December 5, 1957, at his home, Sedgefield, Co. Durham, James Cecil Vickerman Hindhaugh, M.B., B.S., aged 57.
Mackenzie.—On December 8, 1957, in hospital, John Baird Mackenzie, M.B., Ch.B., of 18, Regent's Court, Park Road, London, N.W., aged 78.
Murphy.—On December 3, 1957, Denys Fitzgerald Murphy, *M.C.*, M.B., F.R.C.S.Ed., Colonel, I.M.S. (retired).
Thomson.—On December 10, 1957, Eric Alexander Thomson, M.B., Ch.B., of 90, Pembroke Road, Bristol.
Waters.—On December 8, 1957, Henry Waters, M.B., Ch.B., D.P.H., of 239 Stainbeck Road, Leeds, Yorks.
Whittingham.—On December 6, 1957, in hospital, Josef Karel Rudolf Whittingham, M.D., of Fulston, Alderley Road, Wilmslow, Cheshire.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Inoculation Campaigns and Viral Hepatitis

Q.—*In mass inoculation campaigns what procedure should be adopted to avoid the risk of transmitting viral hepatitis ?*

A.—The ideal to aim at is a fresh syringe and needle for the inoculation of each patient, the day being begun with syringes and needles which have been sterilized in an autoclave or hot-air oven. If they need to be re-used during the same session, immersion of syringes and needles in boiling water for 10 minutes should be adequate. However, even the latter may be impracticable in the time available. If this is so a fresh needle should be used for each inoculation, the syringe being changed only when its contents have been finished. With this procedure there seems to be less risk of transmitting hepatitis to children than to adults.

Pneumoconiosis without Occupational Exposure

Q.—*At post-mortem examination is "simple pneumoconiosis" ever found in persons who have lived for a long time in industrial areas but not been exposed to any occupational dust hazard ?*

A.—"Simple pneumoconiosis" is a descriptive term applied to lungs showing deposits of dust uniformly distributed as discrete foci, and this appears to represent the characteristic way in which retained dust is deposited. Pathologically, the term has not been defined quantitatively and could therefore be used to describe any lung in which dust deposits are observed. In practice, however, the description is reserved for lungs which undoubtedly show considerably more dust than is found in those who have lived their lives in industrial areas but not been exposed to any occupational dust hazard. This is supported by the finding of about 1 g. of carbon in the lungs of city dwellers,[1] whereas the lungs of a group of coal-workers with early simple pneumoconiosis in a roughly comparable age range gave a mean value of 4.6 g. of dust for the right lung only.[2]

REFERENCES

1 Blacklock, J. W. S., Kennaway, E. L., Lewis, G. M., and Urquhart, M. E., *Brit. J. Cancer*, 1954, **8**, 40.
2 King, E. J., Maguire, B. A., and Nagelschmidt, G., *Brit. J. industr. Med.*, 1956, **13**, 9.

Familial and Hereditary Factors in Cerebral Palsy

Q.—*What are the main aetiological factors responsible for cerebral palsy in children ? To what extent do these factors predispose to further spastic children in the same or subsequent generations ?*

A.—The main aetiological factors responsible for cerebral palsy in childhood may be classified into three groups—prenatal, perinatal, and postnatal. In the prenatal group abnormalities of development of the brain are responsible for the cerebral palsy, and, while a large number of different types of abnormality have been described, the actual factors responsible for the developmental errors are almost entirely unknown. In a very few cases the abnormality is familial, but in Britain cerebral palsy resulting from any genetically transmitted condition is very rare indeed. The second group results from damage occurring at the time of birth, or just before or just after. The factors concerned are intracranial haemorrhage, anoxia, and kernicterus. The latter results from excessive bilirubin production damaging the brain a few days after birth. None of the perinatal causes have any familial trend apart from kernicterus, which is due to blood incompatibility in almost all cases. There is therefore a possibility of more than one case occurring in a family. Postnatal factors causing cerebral palsy at some time in the early years of childhood are various and may result from vascular accidents, injury, or infection, as in meningitis.

It is reasonable to say that cerebral palsy is not familial, and to reassure any parent who has a child with cerebral palsy that there is very little chance of a subsequent one being affected.

Retracted Testicles

Q.—*A boy now aged 11 was born with both testes in the scrotum, but after about the age of 5 he grew quite quickly and both testes have been pulled up to the external inguinal ring, with no sign of resuming their usual position as yet. Are they likely to descend again at the onset of puberty, or is active treatment needed ?*

A.—This story is somewhat unusual, and it is difficult to understand just why the testicles, which were in the scrotum for the first years of life, are now lying at the external inguinal ring. It is possible that they are drawn up at times, but descend normally at other times. It is, of course, normal in animals to be able to retract the testicles, and some vestige of this remains in the human. At certain times, particularly if a child is cold, the testicles tend to be drawn higher up, and it is possible that something of the sort is happening in the case of this boy. It is most unlikely that any treatment is necessary.

Composition of Detergents

Q.—*What is the chemical composition of household detergents ?*

A.—In common with many other commercial products of all kinds, the precise formulae of household detergents are not published, nor is the information available to the public in the Patent Office. One of the biggest manufacturers of household detergents has supplied the following information about the composition of most granular household detergents: alkyl benzene sulphonates, 20–30% ; complex phosphates, 30–40% ; sodium perborate, *c.* 10% ; carboxy methyl cellulose, *c.* 1% ; optical whiteners, *c.* 0.05%.

To a bona fide inquirer a manufacturer would supply further information on the properties of the ingredients used or the results of research concerning their effects in use. Detailed information on formulation would be disclosed only under conditions where the manufacturer's interests are properly safeguarded.

Autotransfusion of Peritoneal Blood

Q.—*Where there has been massive intraperitoneal bleeding as from a ruptured spleen or liver, should the blood recovered from the peritoneal cavity be returned to the circulation ? If so, what is the technique, and are there any special hazards to guard against ?*

A.—Massive intraperitoneal bleeding may result from a ruptured ectopic pregnancy or abdominal injuries such as rupture of the liver or spleen.

Where supplies of donor blood are available it is best to treat the haemorrhage with them, but if such supplies are not available an autotransfusion of the blood from the peritoneal cavity may be performed. There are, however, two definite contraindications. One is any evidence of infection, as may occur if there is an associated injury to a hollow viscus, and the other is when the haemorrhage has been present for more than eight hours, because after this time the blood in the peritoneal cavity will have broken down to an excessive extent. The technique is to remove the blood from the peritoneal cavity and place it in a sterile container, mixing it with 3.8% sodium citrate in the proportion of 200 ml. to each litre of blood collected. The citrated blood is then filtered first through several layers of sterile gauze and then through one of the filters

used in the standard transfusion donor set. Carried out in this way the method is satisfactory, but, as stated, it has been largely replaced by the use of blood from donors because of the added safety and convenience.

Chest Injuries and Angina Pectoris

Q.—*Is there any evidence that chest injuries induce angina pectoris, or bring on this condition sooner than would occur naturally?*

A.—There are many instances on record of blows in the region of the heart causing damage to the myocardium or coronary arteries. Myocardial contusion may occur, with electrocardiographic patterns resembling those of cardiac infarction. Also, damage to the coronary arteries may cause angina of effort or thrombosis with myocardial infarction. It follows that trauma to the praecordium may bring on angina sooner than it might otherwise appear.

It must be borne in mind, however, that many chest pains following injuries involving the region of the heart are not of cardiac origin at all, but may form part of a traumatic neurosis.

Is Early "Potting" Harmful?

Q.—*I understand that present-day opinion is opposed to early "potting" and training of babies in cleanliness. What harm is this believed to do, and what is the evidence for such belief?*

A.—It is true to say that some psychiatrists are opposed to early potting of babies on the grounds that it may lead to subsequent refusal of the baby to use his pot. I disagree with this. There is nothing against beginning to pot the baby early (e.g., at 1–2 months), provided that the baby is never forced to sit on it against his will: there is a lot to be said for it, because it reduces the number of dirty and wet napkins. It is not early potting which does harm, but compelling a child to sit on the pot when he is screaming to get off, and punishment and fuss when accidents occur. Mothers should understand that emptying of the bowel and bladder when babies are potted in the early months is entirely reflex and unconscious: voluntary control does not begin till about 15 months of age in an average baby.

I dislike the term "training of babies" in cleanliness. Mothers in fact cannot train them. As soon as the nervous system is sufficiently mature, babies will begin to tell the mother when they want to use the pot, and, if they are helped when they are asked, they will then acquire clean habits. They are not "trained" to do this. Determined efforts to train a child are likely to do nothing but harm, and may well lead to the child refusing to use the pot at all.

Hydrogen Peroxide in Cancer Therapy

Q.—*What is the value of oral, locally infiltrated, or intravenous hydrogen peroxide in the treatment of human malignant disease?*

A.—Oral, locally infiltrated, or intravenous hydrogen peroxide has, as yet, no proved value in the treatment of human malignant disease.

Holman[1] described an experiment in which rats implanted with the Walker 256 adenocarcinoma were treated by having their drinking water replaced by a 0.45% solution of hydrogen peroxide. On this regime the tumours disappeared in 50 to 60% of cases. The interpretation of these results is difficult, but it is known that this experimental carcinoma is particularly liable to spontaneous regression and the author did not give the results of any control cases, though a further report is promised. There are many substances which produce dramatic regression or even cures of transplantable animal tumours, but more often than not when tried on human tumours they have no effect.

Motawei[2] claimed that he had cured a rodent ulcer by local infiltration of hydrogen peroxide. He also claimed that intravenous injections of 20 ml. of hydrogen peroxide once or twice daily caused a regression of some human tumours and was also an effective treatment for tuberculosis. However, he gave no details of the patients treated and only a scanty description of the technique used. He stated that no ill effects had followed the intravenous injections, but research workers in Britain have found that in animals hydrogen peroxide given intravenously has toxic effects, one of the most important of which is probably the changing of haemoglobin to methaemoglobin.[3]

REFERENCES

1 Holman, R., *Nature (Lond.)*, 1957, **179**, 1033.
2 Motawei, A. M., *A Preliminary Report on a New Chemotherapeutic Agent Effective in the Treatment of Malignancy and Tuberculosis*, 1954. Memphis Press, Cairo.
3 Scott, O. C. A., personal communication.

Trauma and Onset of Myxoedema

Q.—*Over a period of three weeks following a fall in which only minor injuries to the limbs were sustained one of my patients developed very rapidly a typical picture of myxoedema. She is now responding satisfactorily to thyroid medication. Is there any known connexion between trauma, either physical or psychological, and the onset of myxoedema?*

A.—I know of no established connexion between physical or psychological trauma and the onset of myxoedema. Theoretically the shock of the accident could initiate changes in the endocrine system through the influence of emotional mechanisms on the hypothalamus; or local trauma to the neck could be followed by local atrophy of thyroid tissue.

This may be a case of the ordinary spontaneous myxoedema of uncertain cause and the relation to the fall purely a coincidental one. But three weeks is an unusually short time in which to develop typical myxoedema, and the possibility of there being some other cause contributing to the change of appearance has to be considered.

Correction.—Dr. John Fry informs us that he made an error in Table IX of his paper on "Five Years of General Practice" (*Journal*, December 21, p. 1453). The table should read:

TABLE IX.—*Incidence of Acute Otitis Media Per 1,000 at Risk in Age Groups*

0–	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	20–	30–	40+
150	120	150	180	240	300	260	150	100	80	55	5	35	5

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The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

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Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

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